VOLUME 50 NUMBER 5

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1. *Kamman, G. R. (1938), Am. J. Syph., Gonor. and Ven. Dis., 22:638, Sept.*

2. *Spiegel, L., Liefer, W., and Sarason, H. (1941), Am. J. Syph., Gonor. and Ven. Dis., 25:472, July.*

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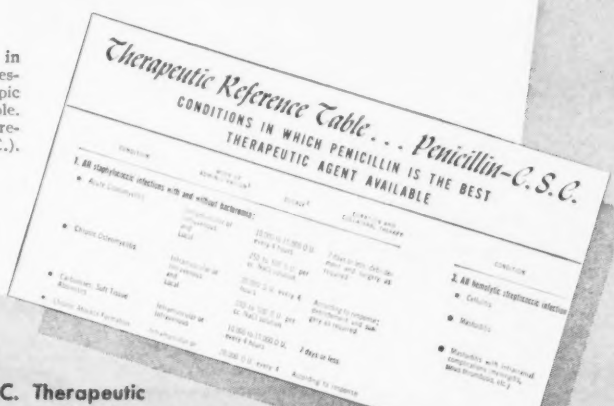
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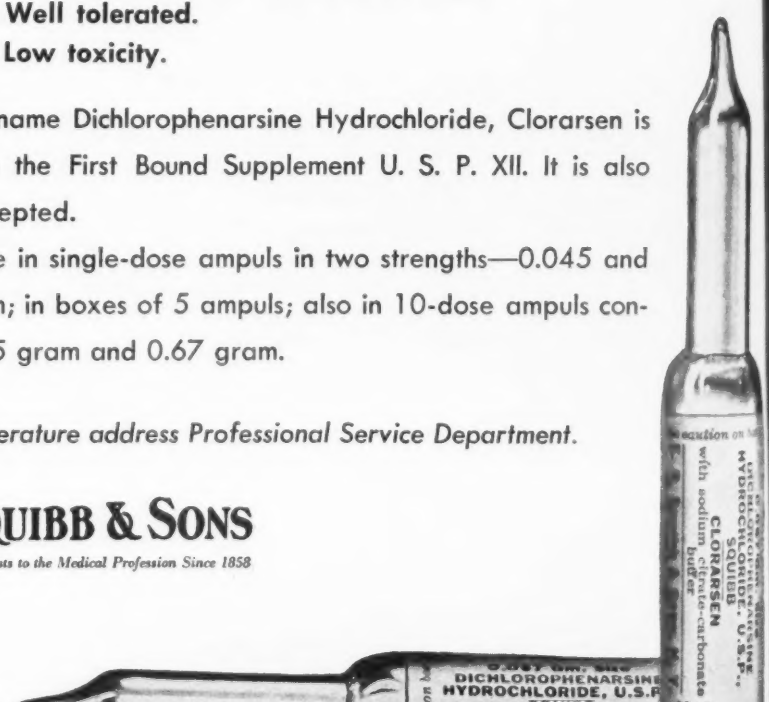

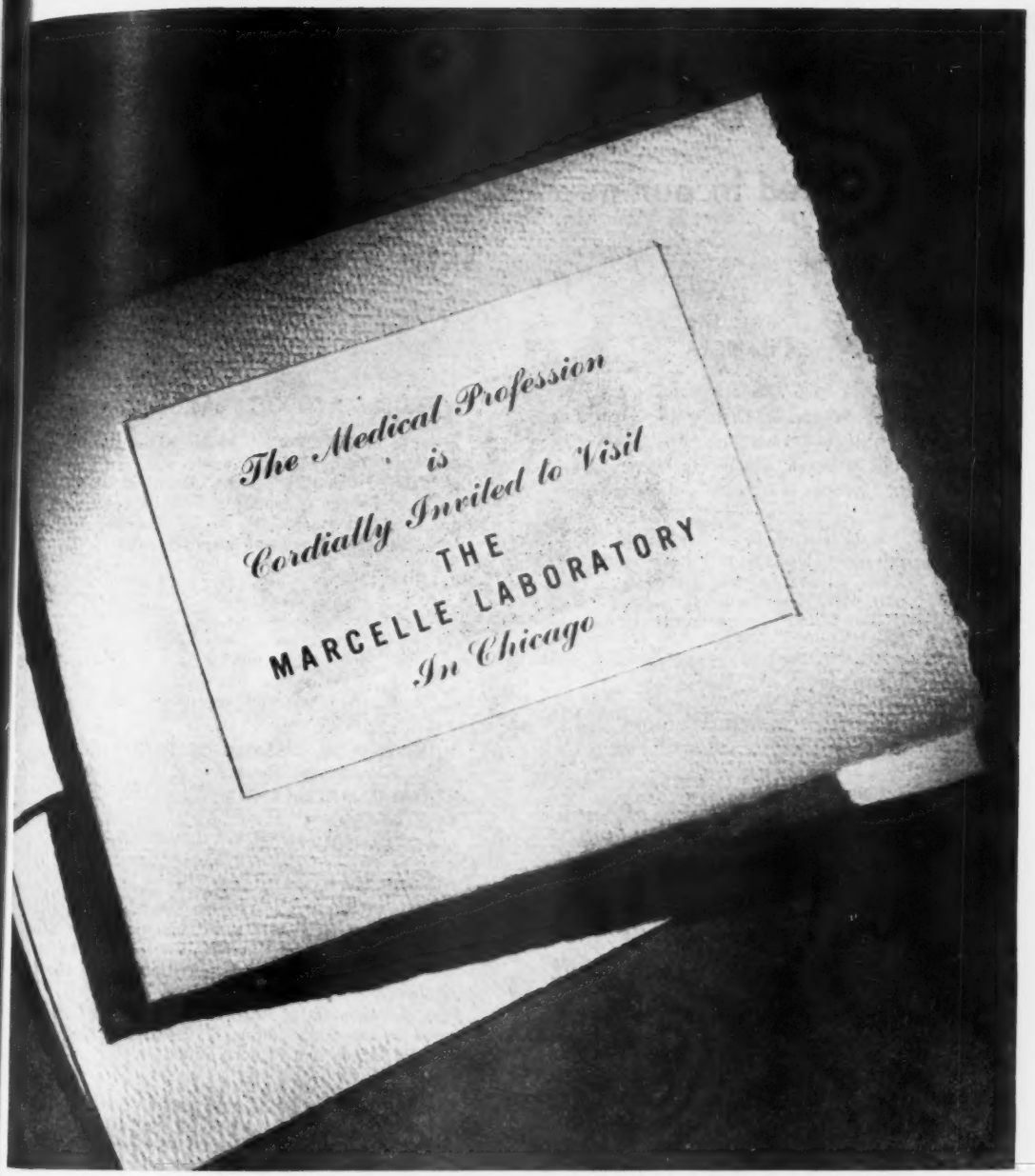

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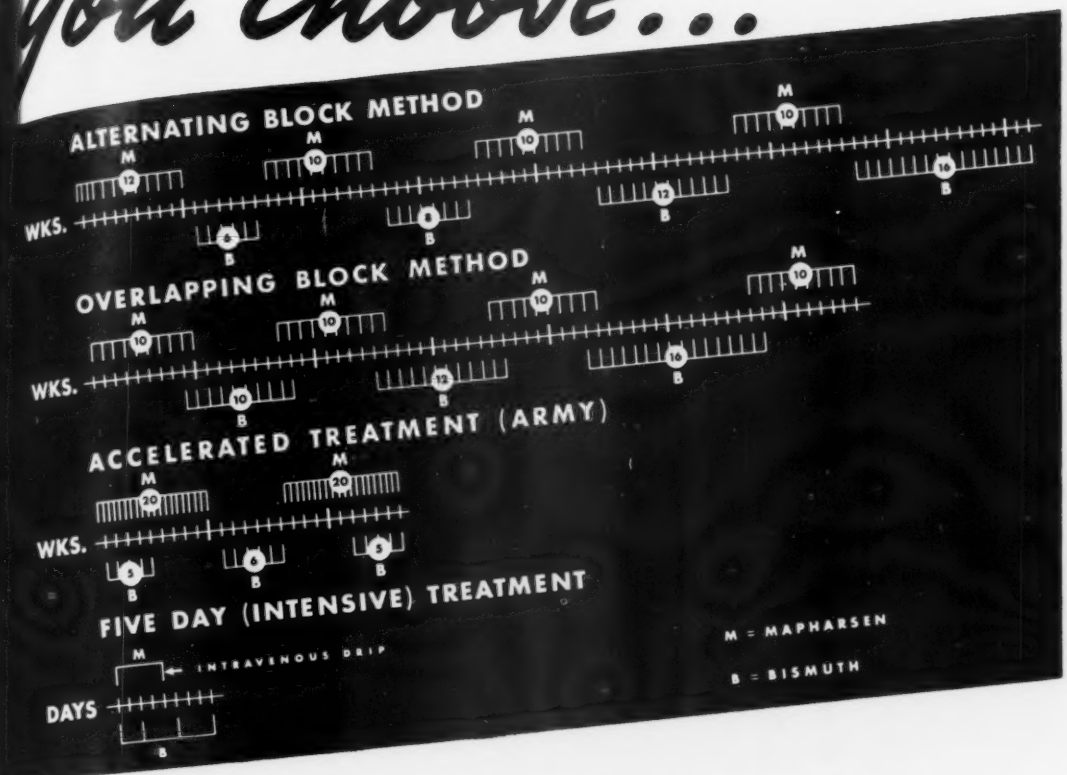

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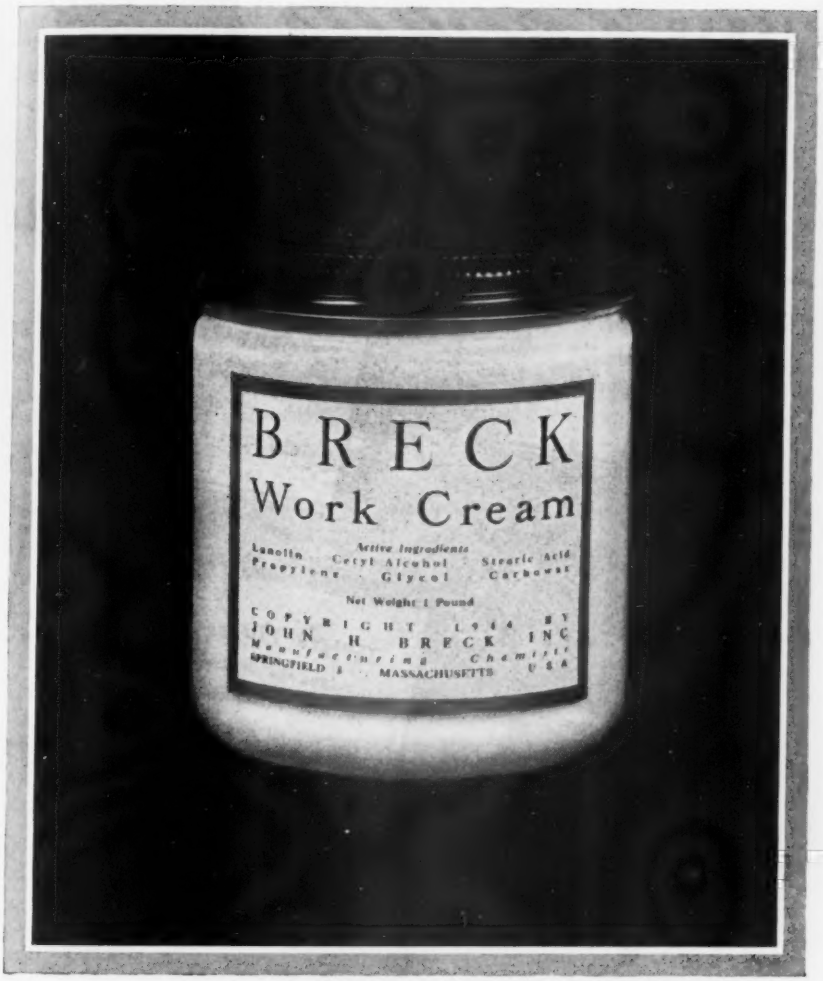

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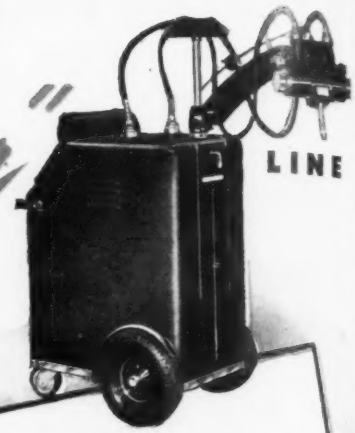

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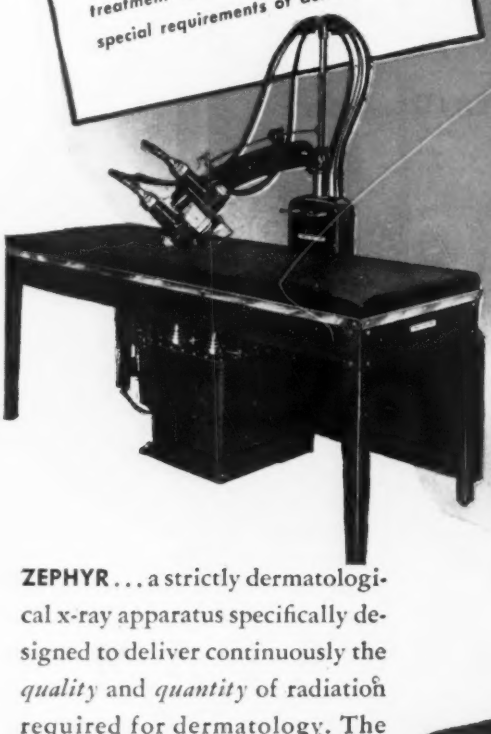

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VOLUME 50 NOVEMBER 1944 NUMBER 5

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HAZARDS OF THE EXTERNAL USE OF SULFONAMIDE COMPOUNDS

E. WILLIAM ABRAMOWITZ, M.D.
NEW YORK

When the sulfonamide drugs are used internally against specific organisms capable of producing serious or crippling systemic disease, certain safeguards are necessary: optimum dosage, alkalinization, dilution, determination of blood concentration, blood counts, etc., to avoid urinary, hematologic and other visceral ill effects. In spite of all precautionary measures, cutaneous and various types of reactions may appear that are considered more or less unavoidable. The administration of sulfonamide compounds in the presence of a major infection, however, is justified regardless of any untoward reactions that may develop.

It is my purpose to discuss the hazards of the local use of the sulfonamide compounds. This topic bears repetition because these drugs are being used more and more in treatment of comparatively minor infections of the skin and orificial mucous membranes. Such preparations may have certain immediate advantages over the older and conventional measures in selected cases. Their indiscriminate use for other local infections of the skin and mucosal orifices is questionable, not only because of the uncertain results but because of the potential hazards that may develop.

Sulfonamide compounds are being used in the form of powder and also are being incorporated in lotions, films, water-soluble creams, ointments and pastes. Preparations suitable for the eyes, ears, nose and throat, vagina and anorectal area are available. First-aid dressings and various confections, also a shaving cream, containing one of the drugs have appeared on the market. In most instances the preferred active ingredient is sulfathiazole, and therefore the present observations are directed mostly against that particular drug. They also apply to the other derivatives, if used in the same way.

Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 21, 1944.

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University, Dr. George M. MacKee, Director.

LOCAL USE OF SULFONAMIDE COMPOUNDS FOR VARIOUS DISEASES

Pyodermas: Impetigo, Ecthyma, Chancroidal Infection. — The dermatitis from sulfathiazole that I have seen was usually in adults affected with impetigo. The cutaneous reaction was more frequent than the dermatitis observed from the use of ammoniated mercury in such cases. According to Klauder,[1] dermatitis from ammoniated mercury is uncommon. There seems to be a contrary impression, but it is not sustained by the enormous amount of ammoniated mercury being used (annual sale of one million packages besides that dispensed on prescription) and the reports of only 12 cases [2] of dermatitis from its use from 1883 to 1942. With due allowance for unpublished cases, the incidence of reaction to this mercurial is extremely low.

Dr. H. N. Cole,[3] in his report for the Council on Pharmacy and Chemistry of the American Medical Association, gave a careful review of the literature on the local use of sulfonamide compounds in dermatology. He advised that such preparations should be used only after the older tried methods have failed and that great care should be exercised not to extend their application over five days at the most. Despite this warning and their nonacceptance as yet in "New and Nonofficial Remedies," such preparations are being used more than ever and with careless abandon.

Of the numerous sulfonamide preparations to be had, microcrystalline sulfathiazole seems to be the most promising, preferably in an oil in water emulsion base. Concentrations not above 10 per cent are considered adequate.

1. Klauder, J. V.: Comment on "Germicidal Soaps," in "Germicidal" Soaps, report of the Council on Pharmacy and Chemistry, J. A. M. A. **124**:1201 (April 22) 1944.

2. Gibel, H., and Kramer, B.: Idiosyncrasy to Mercury Preparations in Childhood: Report of Two Cases of Reactions to 5 per Cent Ammoniated Mercury Ointment and Mercury Bichloride Solution (1:1,000), Am. J. Dis. Child. **66**:155 (Aug.) 1943.

3. Cole, H. N.: The Local Use of Sulfonamide Compounds in Dermatology, J. A. M. A. **123**:411 (Oct. 16) 1943.

There is no denying that such preparations are generally effective against impetigo and also against ecthyma. But there are other factors to be considered besides the immediate cure. If the eruption clears in five days, so much the better. There are evidently cases in which it does not respond in the maximum safe period, else there would be no need of a warning. Some persons may acquire a reaction in less than five days of use of the cream, because they had previously become sensitized. Others who are discharged from treatment may at the time not show any visible reaction, but sensitization may be in the process of developing. The benefits derived from the local use of a sulfonamide compound may be offset in some cases by the possible appearance of a dermatitis that may require prolonged treatment. This, in turn, may render the patient vulnerable to the future use of the drug when it is needed for more important reasons. There is still a further possibility, not altogether remote, that the patient may become resistant to sulfonamide drugs.

Because of these and other unnecessary risks mentioned later, use of such preparations should be restricted to cases in which sensitiveness to mercury exists or in which other adopted measures fail to produce results.

Chancroidal infection responds rapidly to local dusting with sulfanilamide or sulfathiazole powder. Cole has advised the concurrent use of the drug by mouth. A risk of reaction in such cases is justified because of the uniform good results when compared with results of measures previously employed.

Furuncles, Carbuncles, Abscesses, Varicose Ulcers, Secondarily Infected Dermatoses.—Despite their value in selected cases of such dermatoses, the advantages of the local use of the sulfonamide compounds over the older and conventional methods of treatment are not enough to warrant the risk of a reaction from them. There is no way of preventing such reactions in all cases, even if the drug is used for a short period.

Acne Vulgaris, Sycosis Vulgaris, Infectious Eczematoid Dermatitis.—The topical application of the sulfonamide drugs for these dermatoses has been generally ineffective. Apparently the drug has been used internally either alone or in conjunction with its external use for prolonged periods in such dermatoses. Sutliff [4] reported the case of a girl 15 years old who received 15.5 Gm. of sulfathiazole by mouth during a period of thirty-one days for acne vulgaris. Uremia developed, and the patient died shortly thereafter. Fortunately, no fatalities have followed the external use of the drug.

Burns, Eczematous Dermatitis, Dermatophytosis.—Aside from the general measures employed for burns of a major degree and extent, the local treatment at present in favor is the application of sterile petrolatum gauze dressings with emphasis on suitable compression bandages. Heavily infected burns may require the additional internal use of one of the sulfonamide compounds or one of the newer antibacterial biotics. The directions issued by the Medical Division of the Office of Civilian Defense [5] advise caution in the indiscriminate application of sulfonamide drugs in the treatment of burns.

The sulfonamide drugs have no place in the treatment of the various types of uncomplicated eczematous dermatitis. They have no effect on the superficial forms of fungous infection. They are contraindicated for all such dermatoses, including contact and occupational dermatitis, as they usually aggravate the primary dermatitis present. Their use may be required in the presence of superimposed secondary bacterial infection (lymphangitis, cellulitis, erysipelas, etc.). Here the optimal results are obtained by careful dosage by mouth. The topical application of sulfonamide compounds, concurrently or alone, has only a slight favorable advantage over the conventional topical use of wet dressings of solution of boric acid, solution of aluminum acetate, or solution of potassium permanganate, not enough to risk the possibility of an annoying secondary local or general dermatitis from the sulfonamide compounds.

Infections of the Mucosal Orifices and Minor Surgical Injuries.—Eruptions may follow the use of topical applications of sulfathiazole in the form of instillations, ointments and gargles for various infections of the eyes, ears, nose and throat and other orificial areas. The merits of such procedures will not be discussed. The various visible mucous membranes, with the exception of the conjunctivas, are not vulnerable to reactions from the external application of the sulfonamide compounds. The vermilion border of the lips, the lining of the external auditory canal, the balanopreputial fold, the anus and the vaginal labia, however, may become involved with a reaction of the adjacent skin due to the external use of these preparations. This is somewhat analogous to what happens with the external

4. Sutliff, W. D.; Halpern, M.; Griffin, G., and Brown, H.: Sulfonamide Toxicity as a Cause of Death in New York City in 1941, J. A. M. A. **121**:307 (Jan. 30) 1943.

5. Medicine and the War: Civilian Defense—New Recommendations on Treatment of Burns and Wound Infections, J. A. M. A. **122**:816 (July 17) 1943.

se of iodoform. As in the latter instance, protection of the skin where possible, when applying sulfonamide preparation to various mucosal cavities, may prevent the development of a dermatitis of the adjacent skin.

Penetration of the drug into the blood due to local absorption from the mucosa may result not only in a cutaneous reaction but in visceral effects similar to those following internal administration.

The sulfonamide drugs in various pharmaceutic forms are being applied to cuts, bruises and other minor surgical injuries. In addition to the local and generalized dermatitis that may appear, delay in healing and troublesome sanguineous oozing may develop. This will be referred to again.

FREQUENCY OF REACTIONS FROM EXTERNAL USE

Long [6] estimated in 1941 that about 10 per cent of persons who took a sulfonamide compound internally had some kind of reaction from its use. Other observers consider reactions as being much less frequent. There are some recent figures,[7] however, that indicate that Long's estimate is more in keeping with the actual situation. Among these reactions, eruptions of various kinds are a conspicuous feature.[7] The cutaneous and other reactions have a tendency to recur on subsequent use of the same drug but may not recur when another derivative of sulfanilamide is substituted. A small trial dose should be given to determine this.

The dusting of sulfonamide compounds in powder form into various large body cavities gives rise to reactions similar to those seen following the internal use. They are not so frequent, however, unless used in excessive amounts or over prolonged periods.

There is a difference of opinion among various observers as to the frequency of cutaneous reactions from the local application of the sulfonamide drugs. Some of the pioneers in the use of sulfonamide ointments have expressed the belief that cutaneous reactions from such preparations appeared only in an occasional patient.

I discussed this question with the dermatologists with whom I am associated. Dr. George M. MacKee, for instance, told me that he has seen such reactions but that they were infrequent. On the contrary, Dr. Fred Wise stated that he saw on the average about 2 cases a week. Dr. Isadore Rosen said that he usually observed 1 case or more every week. Dr. Howard Fox was of the opinion that dermatitides from the external use of sulfonamide compounds were appearing with increasing frequency—enough to warrant some restriction in the use of such preparations. That such reactions are far from occasional is in accord with my own experience.

Darke [8] in treating 218 different patients with injuries of a minor surgical nature with 5 per cent sulfathiazole cream observed 12 instances, or 5.5 per cent, in which sensitivity developed. Downing [9] has seen 300 serious cutaneous reactions mostly from the external use of the sulfonamide compounds, usually in an ointment base, in cases of uncomplicated industrial dermatitis. Tate and Klorfajn [10] observed 55 cases of dermatitis from sulfonamide drugs, 52 from the external application of sulfanilamide and 3 from sulfapyridine, in a total of 2,280 admissions to the dermatologic department of a British military hospital, during a period of six months. There are other British observers who have also reported a number of such cases. Judging from the correspondence that appeared in several subsequent issues of the *Lancet* following Tate and Klorfajn's article, there is apparently some difference of opinion in other quarters as to the frequency of reactions from the external use of such preparations.

This discrepancy in observations of persons with wide experience is puzzling. The hazards of unavoidable reactions from the internal use of the sulfonamide drugs for a serious illness are justified. The frequency of such reactions may be more or less an academic question. It becomes a matter of importance when such drugs are applied externally for comparatively minor disorders. Here one must weigh the advantages against the possible disadvantages of such procedures over those formerly employed.

Drugs are capable of causing eruptions irrespective of the method of administration. Eruptions from certain drugs appear in practice only from internal use (arsenicals, barbiturates, gold). Drugs employed mainly for their local pharmacologic effect (iodoform, menthol, procaine hydrochloride) may produce local dermatitis but seldom give rise to eruptions when used internally. Certain mercurial preparations like me-

6. Long, P. H., in discussion on Sutliff and others.[4]

7. Dowling, H. F.; Dumoff-Stanley, E.; Lepper, M. H., and Sweet, L. K.: Relative Toxicity of Sulfamerazine and Sulfadiazine, J. A. M. A. **125**:103 (May 13) 1944.

8. Darke, R. A.: Sensitivity to Topical Application of Sulfathiazole Ointment, J. A. M. A. **124**:403 (Feb. 12) 1944.

9. Downing, J. G.: Dermatophytosis and Occupational Dermatitis, J. A. M. A. **125**:196 (May 20) 1944.

10. Tate, B. C., and Klorfajn, I.: Sulphonamide Dermatitis: Sensitization from Local Application, Lancet **1**:39 (Jan. 8) 1944.

tallic mercury, mild mercurous chloride and mercury bichloride produce cutaneous reactions more often when applied externally than when used internally. Other drugs, mostly the organic compounds (quinine, resorcinol and salicylates), produce eruptions from internal use as often as from external application. It is to this last category that the sulfonamide compounds apparently belong. The frequency of the cutaneous reactions that follow their internal use is reported to be from 2 to 10 per cent.[11] The frequency of such reactions from external use should be either about the same or higher, judging from some of the reports previously cited and the increasing resort to the use of such products.

If reactions, particularly from the external use of the sulfonamide drugs, were reported to some central body representing the various national dermatologic societies, then the frequency of such reactions might be arrived at more accurately. On the basis of the number of dermatologists in the United States[12] and on the assumption that each one sees at least 1 new case of dermatitis from the external use of a sulfonamide drug a month, I venture to estimate that the number of such cases yearly runs into many thousands.

Another matter that may require consideration is whether it is advisable to determine any change in reaction capacity of the patient to the drug after discharge from treatment with a sulfonamide preparation, external or internal, although no ill effects were present during the time of treatment. This should give the number of persons in the United States who are sensitized to the compounds.

COMMENTS ON ERUPTIONS ENCOUNTERED WITH EXTERNAL USE

Pathogenesis.—The eruptions from use of sulfonamide compounds, irrespective of the method of administration, are no different in many ways from those that appear from the use of other drugs. With internal use of the sulfonamide drugs erythematous (morbilliform, scarlatiniform, erythema-multiforme-like, pemphigoid, fixed) eruptions may appear. The location of the eruption favors the parts of the body exposed to the sun, as the drugs are photosensitizing. Eczematous dermatitis, sometimes extensive, may appear after the internal use, particularly if an earlier dermatitis had developed from the external use or if an eczematous eruption had been present previously from some other cause. Visceral reactions (blood, liver, kidney) observed from the internal use of the sulfonamide drugs have not occurred from the external use. Fever, conjunctival reactions and erythema-nodosum-like lesions appear usually from the internal use of sulfathiazole.

Most of the urticarial erythematous and eczematous responses are accepted as allergic in nature. Fever and nodose lesions are attributed by some authors to other unknown factors. Some of the visceral effects are considered mostly toxic, while injury to the urinary apparatus is due to irritation and obstruction by crystals of an acetylated compound of a sulfonamide drug formed by conjugation.

The principal reaction from the external use of the sulfonamide compounds is the development of a dermatitis. This at the start in no ways differs from an ordinary contact dermatitis from other sensitizing agents. The sulfonamide drugs, with the exception of some of the alkaline salts, even in a concentration of 50 per cent, are not primary irritants. Miller[13] and others showed that cutaneous reactions are apt to be more severe with concentrated ointments. Of the various sulfonamide compounds which have used, sulfathiazole was the single offender. Others have encountered reactions from different derivatives. Several investigators have found that certain vehicles employed may act as the sensitizing agent.

The dermatitis from the local application of a sulfonamide drug appears first at the site of application and often simulates the cutaneous disease for which it is being used. An impetiginous eruption that is being treated presents an increased number of follicular-pustular lesions; eczema cruris, an increase in the number of papules and vesicles with diffuse redness; an ulcerative lesion, painful granulations. In some cases, the face becomes involved, presenting edema and redness. This usually heralds an extension of the eruption to the trunk with the appearance of erythematous macules, some of the iris type, alone or mixed with papulovesicular and pustular lesions, especially in the intertriginous areas. The eruption may become generalized even though application of the drug is discontinued. Frequent relapses are the rule,

11. Bloom, D.: The Danger of Cutaneous Reactions to Sulfonamides, New York State J. Med. **43**:1499 (Aug. 15) 1943.

12. American Academy of Dermatology and Syphilology: Fourth Annual Meeting in New York, Dec. 14 to 18, 1941, News and Comment, Arch. Dermat. & Syph. **45**:581 (March) 1942. The number of members was given as 825.

13. Miller, J. L.: Use of Sulfanilamide and Its Derivatives in Ointment Form, Arch. Dermat. & Syph. **46**:379 (Sept.) 1942.

sometimes with different types of lesions. Extension into the auditory canals, with involvement of the nostrils, the lips and even the mouth, may occur. Involvement of the scalp may be followed by complete alopecia. Furunculosis may also appear. There may be a rise in temperature, and there may be a complaint of pains in the extremities. This represents a severe type of reaction and requires months before complete recovery takes place. I will cite the 2 following cases as examples:

Case 1.—Mrs. A. G., white and 31 years old, was a primipara in the seventh month. She suffered a sunstroke several years previously, and since then the skin had remained sensitive to the sun. Her past history was otherwise irrelevant. On Aug. 27, 1943, she sustained a second degree burn of her left arm from a hot stove. The local druggist supplied her with a tannic acid in cod liver oil ointment containing 1 per cent sulfathiazole that she used for one week. For the next two weeks she used a 5 per cent sulfathiazole cream given her by her physician. The redness of the burnt area continued to enlarge and was followed on October 1 by an itching eruption on her arms and legs. Another dermatologist, not knowing that she had been applying sulfathiazole, gave her ultraviolet irradiation to the extremities about the middle of October. She was first observed at my office on Oct. 21, 1943. The skin presented macular lesions, of the erythema type, covering almost the entire body, but most conspicuous on the face, chest, arms and legs. The site of the burn on the left forearm was red, edematous and keloidal. The patient was hospitalized. During her hospitalization, a number of recurrences developed, one of which could be explained by the accidental handling of the sulfathiazole cream that I had asked to be brought for identification. The skin over the keloidal area on her left arm participated in these recurrences by showing increased redness and swelling (fig. 1). It was about three months before her eruption subsided. She gave birth later to a healthy boy at term.

Fig. 1 (case 1).—Local flare-up of sulfathiazole dermatitis over a keloidal area of the left arm after accidental handling of sulfathiazole cream by the patient.

I believe that this was a definite case of sensitization to the external and prolonged use of a sulfathiazole cream, aided and abetted by the ultraviolet irradiation. As is the case with the internal use of these drugs, patients applying the sulfonamides externally may also become photosensitive. Epstein [14] showed that the local intracutaneous injections of sulfanilamide produces such an effect. Thus another risk is incurred with the external use of these compounds.

It has been noted that patients who show no ill effects while taking a sulfonamide drug internally run less chance thereafter of acquiring a reaction the longer they keep on taking the drug. I have observed this in 1 patient who took various sulfonamide drugs for over five years for a recurrent lymphangitis of the scrotum. Nevertheless, I do not think it is safe to use the drug for such prolonged periods. Tate and Klorfajn were able to desensitize several of their patients with dermatitis from sulfanilamide ointment by the oral use of the drug. Usually, however, when the cutaneous reaction has subsided from the external application, the use of the drug internally soon after or much later may precipitate a new outbreak more extensive than before.[13]

A redeeming feature about the reactions from the external use of the sulfonamide compounds has been the absence of any serious visceral complications like those appearing from the internal or parenteral use of the drug. This refers to hepatic or renal damage, leukopenia, acute hemolytic anemia and others. This is because little absorption into the blood takes place with local application. The following case, however, may indicate that other organs may not altogether escape even when the drug is used externally.

Case 2.—Miss M. F., a bank clerk 17 years old, presented herself at my office on Nov. 26, 1943, with a

14. Epstein, S.: Photoallergy and Primary Photosensitivity to Sulfonamides, J. Invest. Dermat. **2**:43 (April) 1939.

severe weeping dermatitis of the scalp, face, ears, neck, chest and groins. Five weeks previously an ophthalmologist had prescribed a 5 per cent sulfathiazole ointment and eye drops of a colloidal silver solution for a keratoconjunctivitis of the right eye. The treatment was discontinued after one week when the ocular infection cleared. Two weeks later use of the ointment was resumed because of a recurrence of the conjunctivitis in both eyes. Almost immediately, the eyelids and face began to swell, and although she discontinued use of the sulfathiazole ointment, red and weeping patches began to appear on her scalp, face and other parts of the body. The eruption continued to spread over the entire body, giving the appearance of an infectious eczematous dermatitis. There was a purulent secretion from the external ear canals with crusting of the nostrils. Aphthous-like lesions were present in the mouth. She lost all the hair on her scalp. Although her general condition was good, her pulse was alarmingly rapid—150 per minute. She complained of itching all over the body and of pains in the arms and legs. The urine was normal. The blood picture revealed a normal number of leukocytes, with 24 per cent segmented neutrophils and 68 per cent lymphocytes. An occasional atypical lymphocyte was seen. The rest of the count was normal. The eruption has not entirely cleared at the date of writing. The hair on her scalp has returned. The pains in her extremitis have disappeared. Her pulse is now of normal rate. The white cell differential count still shows a relative preponderance of lymphocytes.

The sulfathiazole ointment in contact with the skin of the eyelids caused the dermatitis. The visceral effects, some of which disappeared with improvement of her eruption and absence of other possible causes, seemed to point to the sulfathiazole ointment. Some of the drug may have been absorbed through the conjunctiva.

In the following cases the reactions were of a comparatively minor nature:

Case 3.—Mrs. V. W., 44 years old, appeared at my office on March 19, 1943. She stated she had been given 12 sulfathiazole tablets, 0.5 Gm. each, for a sore throat to be taken in four days. Two weeks later she received a sulfathiazole ointment for an eczema crust.

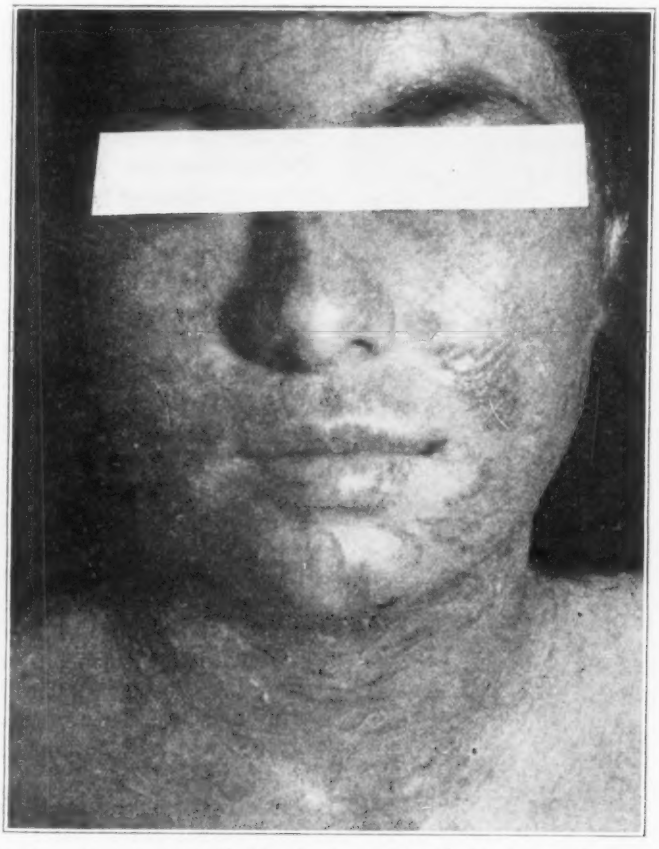

Fig. 2 (case 6).—Erythematosquamous sulfathiazole dermatitis of the face and ears. The chest and upper extremities were similarly involved. Sensitization developed from application of sulfathiazole cream and oral use of sulfathiazole tablets for impetigo of the face. The dermatitis was precipitated by a return to the use of the cream.

The eruption in the latter area spread and became bullous. A diffuse itching erythema developed on her face, ears, chest and forearms. The eruption lasted about one month.

Case 4.—Mrs. V. B., about 40 years old, was first observed at my office on Feb. 3, 1944. She began using a sulfathiazole ointment for a probable impetigo of the left cheek around Christmas time in 1943. She also was using some sulfanilamide drops for the right external ear canal. She presented a weeping red dermatitis of the right lobe. The eruption of the right ear cleared rapidly when use of the ointment and drops was discontinued.

Case 5.—Mr. L. S., 43 years old, came to see me on Feb. 21, 1944. He had cut his left ear lobe and had used sulfathiazole cream for two weeks and then after a short interval for another few days. This last application caused the development of a crusted dermatitis. This cleared in two weeks with use of a bland ointment.

Case 6.—Miss A. de A., 17 years old, appeared at the Skin and Cancer Unit of New York Post-Graduate Medical School and Hospital (service of Dr. I. Rosen) on Feb. 21, 1944. In December 1943 she had impetigo of the face, for which she used a sulfathiazole cream. The eruption not improving, she substituted sulfathiazole tablets for one week. Then, because she kept on getting worse, she started to use the cream again. When seen in February of this year, the entire face, ears, chest and upper extremities presented a red scaly and itching dermatitis with yellowish crusts. It took two months for the eruption to clear. Several blood counts showed a mild secondary anemia with about 3 per cent eosinophils (fig. 2).

Case 7.[15]—E. D., a boy aged 7 years, when observed on Sept. 19, 1942 had patches of impetigo scattered over most of the body. Five per cent sulfathiazole ointment was applied without reaction to all the lesions for five days. On the sixth day the patient awoke with a swelling of the right jaw. He was seen by his dentist, but no cause for the swelling was found in his teeth. The following morning the edema spread to the face, eyelids and prepuce. The edema was soft, with no sign of dermatitis. The impetigo had largely cleared. The swelling disappeared in twenty-four hours after use of the ointment was stopped and a solution of gentian violet substituted. The mother remembered that the child had had a mild dermatitis on the elbows and knees six months previously while taking sulfathiazole by mouth for a threatened mastoiditis. The impetigo cleared entirely in three days of treatment with methylrosaniline.

This is an angioneurotic edema type of reaction. Dennie[16] and Costello[17] reported similar reactions from the internal use of sulfathiazole.

A number of other cases of dermatitis from sulfonamide compounds, mostly in clinic patients, were observed. Although they were charted as sulfonamide dermatitis, they are not recorded here as such, because of the patients' failure to return for investigation.

No patch tests were made in any of the cases cited. The history was considered adequate. No determination of the concentration of the drug in the blood was made. None of the patients has so far had a subsequent attack of dermatitis by either purposeful or accidental exposure to the drug. A relapse of this nature is the best proof available at present for the exact relationship between cause and effect. Failure of recurrence might not be altogether evidence to the contrary.

Histology of Sulfathiazole Dermatitis.—Tedder,[18] in his histologic study of the various types of eruptions from the internal use of sulfonamide compounds, stated that such dermatoses present various stages of inflammation that cannot be differentiated from those produced by sensitization. On the other hand, the dermatitis from sulfonamide compounds precipitated by sunlight presented pathologic changes similar to those seen in cases of arsenical dematitis and of acute lupus erythematosus.

Miescher[19] described the peculiar histologic character of the erythema-nodosum-like lesions following the internal use of sulfathiazole. In the superficial type the infiltration was reminiscent of a small metastatic skin focus seen in septicemia. The deep type presented edema and nodules of small polymorphous histiocytes with polymorphonuclear leukocytic infiltration situated between the cutis and the subcutis. Miescher stated that he believed this to be an inflammatory-granulomatous reaction activated by the sulfathiazole.

There was little opportunity to perform biopsies in all cases of dermatitis as a result of the purely external use of sulfathiazole. It was done in case 6, from a patch of dermatitis on one arm (figs. 3 and 4). The result of the histologic examination was reported by Dr. Wilbert Sachs as follows:

> The vessels of the middle and upper portions of the cutis were dilated, with some focal cellular infiltration about them. There was considerable edema, especially in the subepidermic region, where the capillaries of the papillary bodies were greatly dilated. The overlying epidermis was acanthotic, the rete pegs elongated and the suprapapillary plates thinned. The surface was covered in part by parakeratosis and in part by a large crust. There was a slight intercellular edema of the epidermis. The vessel walls were thinned and in some areas seemed to be broken up. The cellular infiltration was composed of small round wandering connective tissue cells and plasma cells. The acanthosis was like that seen in psoriasis. The area of local necrosis simulated a reaction due to contact with a primary irritant. The vascular changes and focal cellular infiltration indicated a subacute inflammatory process which was of a productive nature owing to the presence of plasma cells.

The histologic conditions are interpreted as indicating that the drug has no selective action on any particular structure of the skin but calls

15. Dr. J. Lowry Miller, of the Vanderbilt Clinic, supplied the history of this case.

16. Dennie, C. C.: Angioneurotic Edema and Dermatitis Venenata-Like Lesions Due to the Oral Administration of Sulfathiazole, J. A. M. A. **120**:197 (Sept. 19) 1942.

17. Costello, M. J.; Rubinowitz, A. M., and Landy, S. E.: Sulfonamide Therapy in Dermatology: Observations in Two Hundred and Sixty-One Cases at Bellevue Hospital, New York State J. Med. **42**:2309 (Dec. 15) 1942.

18. Tedder, W. T.: Toxic Manifestation in the Skin Following Sulfanilamide Therapy, Arch. Dermat. & Syph. **39**:217 (Feb.) 1939.

19. Miescher, G.: Sulfathiazole Eruption and Sulfathiazole Fever, cited by Sulzberger, M. B., and Baer, R. L.: The Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1943, p. 81.

forth a fairly severe productive inflammatory reaction in the cutis with eczematization of the epidermis. It does this even in distant areas where the ointment has not been applied. This may explain the relapses and the slow clinical recovery almost characteristic of a sulfonamide dermatitis. A study of other cases, however, is necessary to determine whether they are similar in nature.

Prevention. — Wider dissemination of the knowledge of reactions and their consequences from the external use of sulfonamide compounds is desirable.

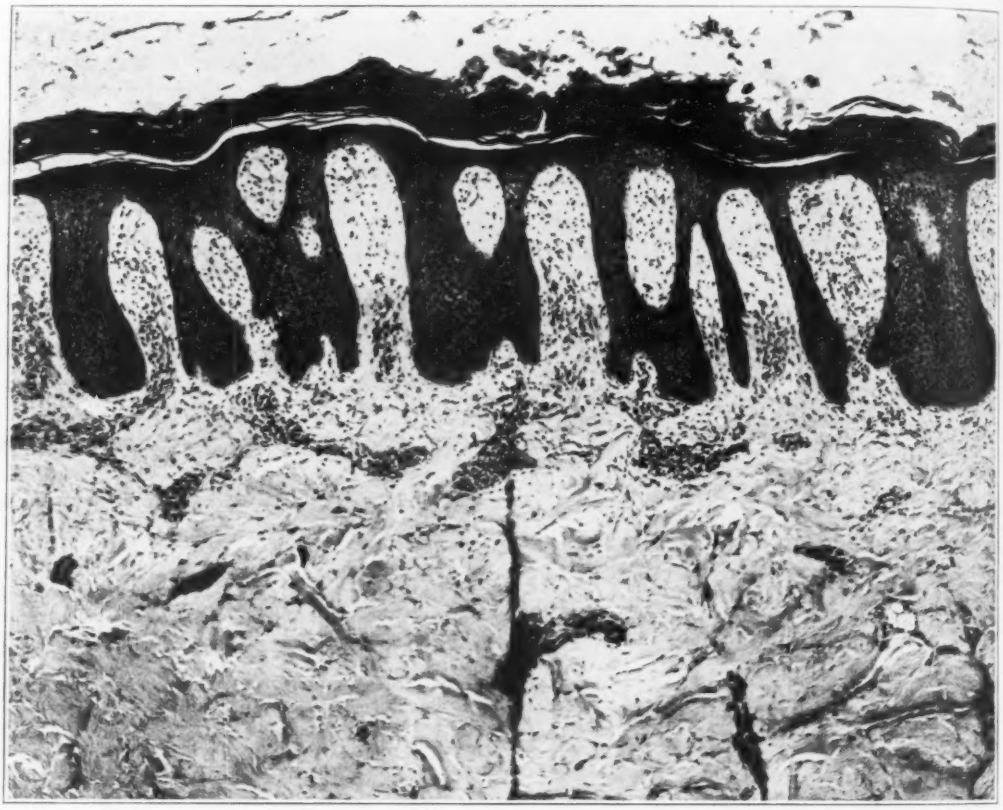

Fig. 3 (case 6).—Biopsy specimen (× 75) from dermatitis of left arm from use of sulfathiazole cream for impetigo of the face. Note the dilated vessels of the papillary bodies and of the middle and upper portions of the cutis and also the edema in these areas. There are acanthosis, parakeratosis and crusting of the epidermis.

Following the reading of the paper by Bloom [11] the Section of Dermatology and Syphilology of the New York State Medical Society at the annual meeting on May 6, 1943 passed the following resolution, introduced by Dr. Howard Fox:

WHEREAS, Repeated administration of sulfonamides either internally or locally may sensitize an individual to these drugs and thereby preclude their future use in serious diseases, such as pneumonia; therefore, be it

Resolved, That the Section of Dermatology and Syphilology go on record as strongly disapproving the indiscriminate use of sulfonamide drugs in relatively harmless diseases of the skin which can be satisfactorily treated by equally efficient drugs; and be it further

Resolved, That the Section condemn the use of prepared dressings containing sulfonamide drugs which are sold promiscuously to the laity.[20]

Likewise, the Department of Health of the city of New York on Aug. 31, 1943 amended Section 118 of the Sanitary Code to require a physician's order for sulfonamide drugs, not only for internal use but for external use whether powder, ointment or sprays.[21] These restrictions apparently do not apply to first-aid dressings containing sulfonamide compounds.

It is apparent from some of the histories mentioned and also from reports of others that changing from internal to external use of the drug or contrariwise or applying the drug over a prolonged period or intermittently is conducive to the development of sensitization.

Ultraviolet irradiation or exposure to the sun while such preparations are in use should be

20. Abuse of Sulfonamides, editorial, New York State J. Med. **43**:1497 (Aug. 15) 1943.

21. Drugs, Devices and Cosmetics, Article 8, Sanitary Code, City of New York, Section 118 as amended Aug. 31, 1943, Quart. Bull., New York Dept. Health **11**:52 (Dec.) 1943.

...ided. Kelly and Dowell [22] believe that roentgen rays and sulfonamide compounds are incompatible. The one may inhibit the action of the other, and untoward effects may result. This raises the question whether it is safe to apply roentgen therapy when a sulfonamide drug is being used externally. The use of local anesthetics of the procaine series and the chemically

open wounds they may encourage bleeding.[24] Delayed healing time of surgical noninfected wounds has also been attributed to the local therapy with sulfonamide drugs.[25] This, however, does not detract from their great value when used internally or when used concurrently with external application in wounds that are heavily infected.

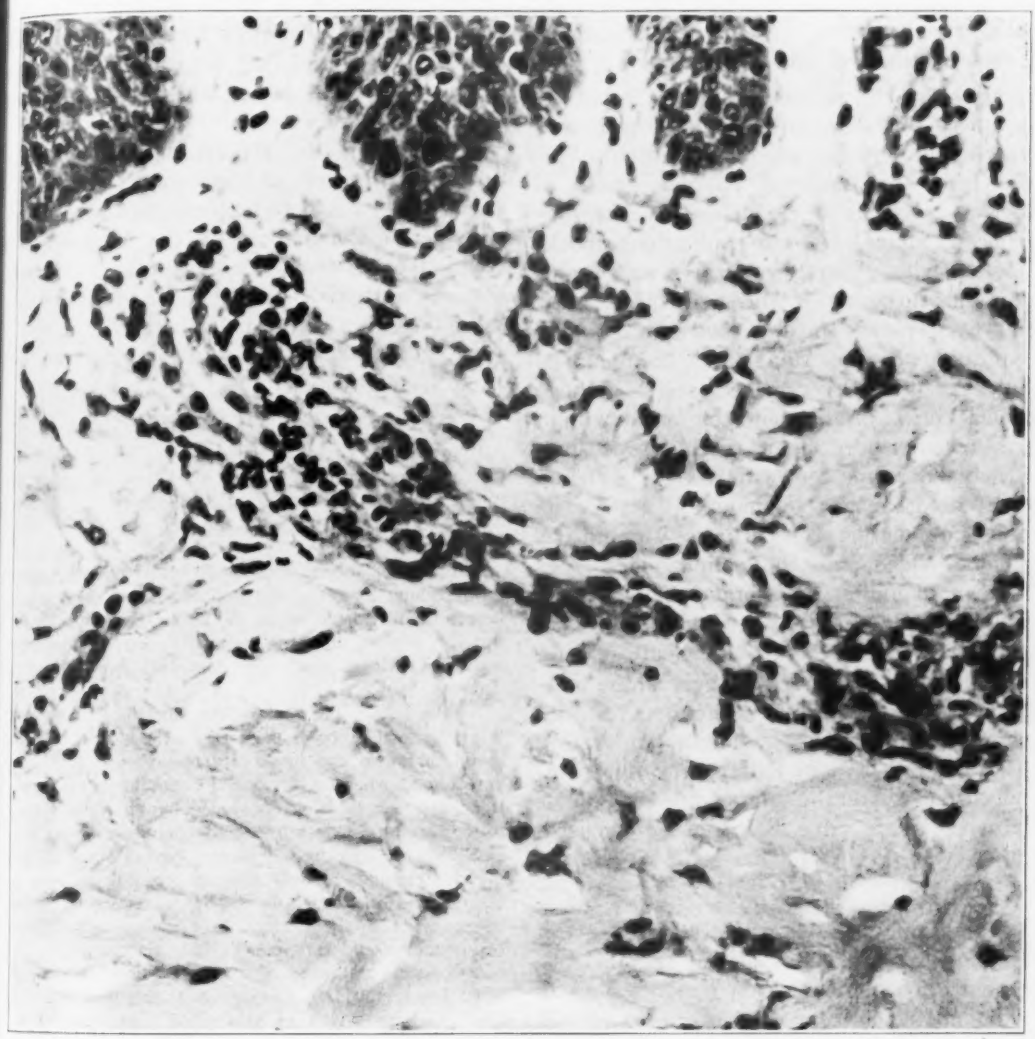

Fig. 4 (case 6).—Higher power magnification (× 135) of a portion of figure 3. Note the thinned vessel walls in the cutis seemingly broken up in some areas. Small round cells, wandering connective tissue cells and plasma cells comprise the cellular infiltration.

...related vitamin paraaminobenzoic acid may inhibit the antibacterial effects of the sulfonamide compounds.[23]

The sulfonamide compounds have been shown to cause hemolysis in vitro. When applied to

Other drugs with photosensitizing properties, like the barbiturates and gold, when used with sulfonamide drugs applied either externally or internally, may intensify the reaction of photosensitization.

22. Kelly and Dowell, cited in Sulfonamides and Roentgen Therapy, Queries and Minor Notes, J. A. M. A. **119**:853 (July 4) 1942.

23. de Waal, H. L.; Kanaar, A. C., and McNaughtan, J.: Antisulphanilamide Action of Procaine in Vivo, Lancet **2**:724 (Dec. 19) 1942.

24. Pelner, L.: Bleeding Following Application of Sulfonamides to Open Wounds, Queries and Minor Notes, J. A. M. A. **125**:178 (May 13) 1944.

25. Bick, E. M.: Observations on the Topical Uses of Sulfonamide Derivatives, J. A. M. A. **118**:511 (Feb. 14) 1942.

Dermatitis has been seen by a dermatologic colleague from the use of a sulfathiazole first aid dressing. A death from tetanus has been reported [26] following a smallpox vaccination on which such a dressing was applied.

Household products not used for medicinal purposes may or may not have all the ingredients listed on the label. In view of this, it is often misleading to state that a person has had no previous exposure to a sensitizing chemical except after the most detailed investigation.

Treatment.—It is unnecessary to state that the local application of a sulfonamide preparation should be discontinued and the substance removed from the skin and possible places of contact as soon as a cutaneous reaction has developed. Suitable topical applications should be applied with general supportive and symptomatic measures, as conditions require.

The liver plays an important part in the detoxification of the sulfonamide compounds. Injection of crude liver extract seems to have a beneficial effect on the well-being of the patient and is recommended as a routine procedure. This may be reenforced with 100 to 200 mg. doses of ascorbic acid by mouth daily, for its possible antiallergic properties. Vitamin A should be added, for the sulfonamide drugs are known to inhibit the storage of vitamin A in the liver.

The diet should be light, with plenty of fruit juices. In cases of a severe generalized dermatitis, with constitutional symptoms, continuous intravenous drip with solution of dextrose may be helpful. The inhibiting action of paraaminobenzoic acid on the sulfonamide compounds has proved of little value in preventing or curing reactions from these compounds.[27]

SUMMARY AND CONCLUSIONS

There are innumerable preparations containing sulfonamide compounds, usually sulfathiazole, advocated for external use on minor lesions of the skin and orificial mucous membranes.

Such preparations generally shorten the duration of impetigo, ecthyma, chancroid and possibly other types of primary and secondary pyodermas.

This advantage, while of some immediate value, is offset by the subsequent complications that may appear in these as well as other dermatoses (eczematous eruptions, varicose ulcers, burns and minor surgical injuries) and minor infections of the mucosal orifices. These complications are: (1) development of a local or generalized dermatitis (allergic sensitization), (2) appearance of photosensitization to sunlight and ultraviolet rays; (3) interference with the action of the roentgen rays; (4) delay in wound healing time; (5) local sanguineous oozing; (6) interference with the action of sulfonamide compounds by local anesthetics of the procaine series and the chemically related vitamin paraaminobenzoic acid; (7) resistance to sulfonamide therapy; (8) rendering the patient vulnerable to the subsequent use of the drug when most needed.

Observations and reports indicate that reactions from the topical application of the sulfonamide drugs are more frequent than is suspected.

Wider dissemination of the knowledge of reactions and their consequences is desirable.

Some restrictions should be adopted to prevent the indiscriminate use of sulfonamide ointments and other pharmaceutic forms for external use.

853 Seventh Avenue.

ABSTRACT OF DISCUSSION

DR. HAROLD N. COLE, Cleveland: Dr. Abramowitz' paper is most timely. It is this type of paper that might well be released by the Association to *Science Service* in order to reach the lay public on a large scale.

The sale of sulfonamide compounds over the counter is increasing by leaps and bounds. Now their use has been so well imprinted on the public consciousness that the lay person demands them for any cutaneous ailment. The results of this are well known to every dermatologist.

As the author has shown, the situations under which the individual becomes exposed to these compounds are becoming more and more bizarre—witness their incorporation in shaving creams. Unfortunately, many of them are due to their local use by physicians, thanks to the zealous endeavors of the detail man.

Moreover, this by no means covers them all. To give an example: A detail man for a drug house had been in the custom of visiting physicians and, to show the ease of application of his particular sulfonamide compound, would rub some of it in on his hands. This practice was followed for a long time. Some time later he acquired a disease of the upper respiratory tract, and his physician prescribed a sulfonamide drug internally. There was an immediate localized reaction and a generalized dermatitis.

All of us are familiar with such cases, and undoubtedly there are many that are not seen by the dermatologist and that are not properly diagnosed.

In my estimation, careful study would show that the frequency of such reactions is far higher than one can imagine. The members of the medical profession are indebted to the efforts of their New York colleagues for their efforts to put this matter before the public.

Moreover, a paper of this type should be placed in *The Journal of the American Medical Association* in order to reach as many physicians as possible.

DR. JACOB H. SWARTZ, Boston: First of all, I want to mention that I happen to be one of the victims that used the shaving cream and found out I was using sulfathiazole. I did not know it until Dr. Abramowitz' paper informed me of the fact.

26. Smallpox Vaccination: A Reminder, editorial, J. A. M. A. **123**:486 (Oct. 23) 1943.

27. Strauss, E., and Finland, M.: Failure of Para Aminobenzoic Acid to Inhibit Sulfonamide Rashes and Fevers, Am. J. M. Sc. **201**:730 (May) 1941.

I want to mention 2 particular cases. The first was that of a pharmacist in one of the hospitals, who was preparing sulfathiazole ointments and using the powder. He was seen with an eruption on his arms and face and swelling of the eyelids, a picture of contact dermatitis but with no history of contact. We suspected various drugs. He was an old man, who had been in the pharmacy of the hospital for years. Finally, he himself put the question. He said, "You know, I have been using a good deal of powdered sulfonamide drugs in preparing ointments, and every so often (the same thing Dr. Cole mentioned) I would smear a little ointment on my skin to find out how soft and soothing it was and what a good base it was."

He had a dermatitis which turned out to be the result of the contact, either as a dust or powder or in an ointment. But the eruption was severe and started on his face.

The other case is that of a man who used sulfa nose drops containing a sulfonamide compound for an infection of the respiratory tract. A few weeks later he contracted pneumonia and he was given a sulfonamide drug. A severe exfoliative dermatitis and anuria developed, and he died. His pneumonia, I understand, had cleared, and he died from the use of the sulfonamide drug. I believe that the nose drops acted as a sensitizing agent.

Dr. Paul E. Bechet, Elizabeth, N. J.: Dr. Abramowitz' paper is a timely and valuable contribution to the subject. Of course, induced sensitivity from the external use of the sulfonamide compounds is well known to dermatologists, but this does not hold true of the general practitioners, who use these drugs externally not by the pound but, figuratively, by the ton. That even the smallest amount of a sulfonamide drug can induce sensitivity was well brought out in the case of a private patient with a small furuncle in his nose, for the relief of which I prescribed an ointment consisting of 10 per cent sulfathiazole in an oxycholesterol-petrolatum base (aquaphor). Not more than a grain or two of this ointment was applied daily to the furuncle for not more than four days, at which time the furuncle was apparently well. There was no local reaction from the sulfathiazole. Ten days later another small furuncle developed on the arm, to which he applied the same ointment; twenty-four hours later the area treated was covered with a severe vesicular dermatitis, which took several weeks to subside. A patch test with the same ointment on normal skin at a later date elicited a strongly positive reaction, which presented the same type of vesicles as those which had occurred on the furuncle on the arm. The case proves that induction of sensitivity can be brought about by even infinitesimal amounts of a sulfonamide drug. In view of this fact, it is interesting to speculate as to whether or not the use of the enormous quantities of the sulfonamide compounds in powder form, both in wounds and externally, in the present war has induced sensitivity among the wounded men.

Dr. J. Harper Blaisdell, Boston: I wish to call attention to the fact that this type of dermatitis can be acquired by what I term the indirect method. If one questions a patient as to whether he is using or coming into contact with a suspected irritant, his reply is always in terms of whether he is applying that irritant to himself. He never takes into account the question of whether he may be applying that irritant to some one else.

The point is illustrated by the case of a physician who last January barked his shin, got a little secondary dermatitis and applied some sulfathiazole ointment and the lesion healed. He presented himself at my office in March with what was evidently a generalized sulfathiazole dermatitis, but said that he had not used any sulfathiazole. It was not until after considerable discussion that it evolved that daily he was preparing dressings and applying them to patients. He spread the sulfathiazole ointment with a throat stick on the dressing and applied it to the patient. Inevitably he got a little ointment on his hands. He rubbed his hands together to remove it, and thus massaged the sulfathiazole into his own skin. That simple indirect method was the source of his trouble.

This questioning of patients with regard to the use of irritants on others than themselves applies to other irritants. I have not, curiously, seen this same thing happen, as it ought to, among nurses, industrial nurses, industrial workers or even doting parents, but I think that cases of this type will be encountered.

Dr. Wiley M. Sams, Miami, Fla.: The effectiveness of sulfonamide preparations in the treatment of pyogenic infections has led to their ready acceptance in communities where there exists a high incidence of impetigo and ecthyma. As indicated in the paper by Dr. Duemling, pyogenic infections are exceedingly common in regions where both the humidity and temperature are high. In my community, impetigo and ecthyma are so common that there is scarcely a drug store which does not have its favorite remedy to be sold over the counter for the treatment of these disorders, usually under some ingenious and catchy trade name. The introduction of sulfonamide preparations has had one good side effect, namely, to crowd most of these remedies from the market. The national drug houses have stepped in to supply a substitute which is now extensively used.

Ecthyma, especially in children, is so prevalent in the southern part of Florida that it is locally and widely known as "Florida sores." This might be added as a synonym for tropical ulcer and desert sore. I have been informed by a veteran of the Boer War that in his day in South Africa they were called "Veldt sores." No doubt many other local names are used. In a warm and humid climate, the lesions are much more recalcitrant to treatment, and the effectiveness of sulfonamide compounds in comparison with that of other drugs makes one willing to risk the chances of contact dermatitis in order to achieve the advantages of its greater therapeutic efficiency.

In the past few years I have had the opportunity to observe the increasing incidence of contact dermatitis from sulfonamide medications, prescribed both by physicians and, more commonly, by the druggist at the corner store. It has been my good fortune not to observe any fatal case as a result of their local use nor to encounter any person who has had serious complications other than extended periods of disability from generalized dermatitis. A review of cases of contact dermatitis observed in the past year reveals that in 5 per cent of cases in which the causal agent was known the eruption was a result of sulfonamide preparations. With continued and extensive use of the drugs, this incidence will no doubt become greater, and the need for a similar product, which is an effective topical agent but not a common cause of contact dermatitis, is at once evident.

Dr. Carroll S. Wright, Philadelphia: I might say there is an excellent and comprehensive article by one of our members, Dr. Donald Pillsbury, in a recent number of the *British Journal of Dermatology*, which I think is well worth reading.

PARTIAL ALBINISM AND NYSTAGMUS IN NEGROES

REPORT OF TWO CASES

LIEUTENANT COLONEL L. J. A. LOEWENTHAL
SOUTH AFRICAN MEDICAL CORPS

The term "partial albinism" is properly used only of persons in whose skin the pigment content is universally reduced though not completely absent; "albinoidism" is the correct designation for patchy congenital leukoderma (piebald Negro). In the literature one finds references to "yellow" and "red" (xanthic) Negroes, and the connection of their abnormality with albinism is inferred from their family histories. In the 2 cases herein reported there is presented further evidence of the relationship between albinism and xanthism by the fact that both men had congenital nystagmus not referable to an absence of pigment from the eye. Such nystagmus is, of course, an integral part of the picture of albinism.

XANTHISM

Xanthism was originally described by Turner,[1] and it has been discussed by Pearson, Nettleship and Usher [2] and Stannus.[3] Strictly, the term is used of Negroes whose skin and hair have a reddish color, but some authors have applied it to yellow Negroes who, without admixture of white blood, show the muddy color often seen in mulattoes. Stannus has reasonably held that the light skin is not a pigmentary abnormality unless the hair and irides are also deficient in pigment. That white, yellow and red Negroes appear not only in the same regions but in the same families is shown by the family tree of Turner's case (fig. 1).

It is significant, too, that Meirowsky [4] has recorded an abnormally high incidence of red-haired members in European families which have produced albinos.

A description of xanthism is unnecessary, as case 1 presents all the typical features; it is noteworthy that Pearson, Nettleship and Usher described pigmented spots on the ears, cheeks and clavicular and axillary regions of both their patients. The association of congenital nystagmus has, to my knowledge, been reported only by Stannus in 1 Negro with doubtful xanthism and in 1 yellow Negro.

REPORT OF CASES

CASE 1.—The patient was a West African Negro from southern Nigeria, aged 24. His parents and all thirteen siblings were normal Negroes, and there were no cases of albinism in his village. He had no children. He stated that he had seen albinos and xanthic Negroes at a big town 120 miles (190 kilometers) from his home. He dated his abnormalities from infancy. His mental and physical states were normal. His features were distinctly negroid.

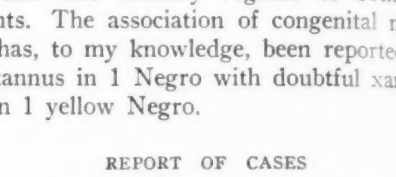

Fig. 1.—Family tree of Turner's case.

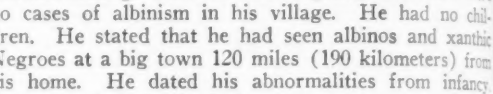

Fig. 2.—Family tree, case 2. It will be seen that members of the families of both parents show pigmentary abnormalities. The possibility that the patient's parents are blood relatives cannot be ruled out, as this state of affairs is common in rural African communities.

The skin was everywhere of a bright copper color, the palms and soles being light yellow. Its texture and secretions were normal. Scattered dark brown lentigines, 2 to 4 mm. in diameter, were present on the cheeks, chest, back and abdomen. The scalp and pubic hair was of the normal "woolly" type but appeared to be of a dull ginger color; on close examination it was found to consist of bright gold and of black hairs, roughly in the proportion of three of the former to one of the latter. There was complete absence of visible pigment from the mucous membranes and nail beds.

The patient stated that he could formerly read but that his vision was failing. Examination by an ophthalmologist (Major Fine, South African Medical Corps) was reported as follows: "The vision of both the right and the left eye is less than 6/18. The right pupil is

1. Turner, G., cited by Meirowsky.[4]
2. Pearson, K.; Nettleship, E., and Usher, C. H.: A Monograph on Albinism in Man, London, Dulau & Co., 1911.
3. Stannus, H. S.: Anomalies of Pigmentation Among Natives of Nyasaland, Biometrika **9**:333, 1913.
4. Meirowsky. E.: Idiotypische Pigmentanomalien, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 4, pt. 2.

slightly eccentric, displaced upward and inward. The color of the iris is reddish brown; the reactions are normal. No abnormality is noted in the media or the retina, where a normal amount of pigment is seen. There is a coarse nystagmus of the congenital type in both eyes."

Histology.—A biopsy of skin from the back of the right hand showed a normal structure, with pigment present in the amount and distribution of that seen in a sunburnt European. Professor Paul Balog, of Cairo, Egypt, examined a portion of the tissue and confirmed the identity of the pigment with melanin. There were no coarse clumps of melanin as in the normal Negro skin, and the pigment appeared as a finely divided golden deposit. It was not possible to investigate the dopa reactivity of the skin.

CASE 2.—This patient was a West African Negro from southern Nigeria. His age was unknown, but he appeared to be in the early twenties. He belonged to a different tribe than the first patient did, and he lived several hundred miles away from the latter's village. In his own village there was one albino, who, he stated, was not related to him. He had never seen a person with partial albinism outside his own family. Particulars of his immediate relatives are given in figure 2. His mental and physical states were normal; his features, distinctly negroid.

The skin was universally clay colored. There were lentigines present on the cheeks, clavicles and chest and in the axillas. The scalp hair appeared black, but on close examination one could see that about a quarter of the hairs were of a golden color. A few of them were golden at the terminal end and black at the root, and an approximately equal number showed the reverse appearance. There was complete absence of visible pigment from the mucous membranes and nail beds.

The vision (right and left) was less than 6/18. The pupils were normal. The irides were hazel colored, and the reactions were normal. Ophthalmoscopic examination showed a normal pigmentary appearance. There was a coarse nystagmus of the congenital type.

COMMENT

That the nystagmus of albinos is not caused by gross deficiency of pigment in the eye is shown by its occurrence in these 2 Negroes, each of whom had an amount of ocular pigment equivalent to that of a European brunet. Both Wolfrum[5] and Seefelder[6] have attributed the causation of nystagmus in albinos to subnormal development of the fovea centralis, and one assumes that nystagmus and albinism are independent anomalies following the same rules of inheritance.

The presence of nystagmus in these men is further presumptive evidence that red and yellow Negroes are examples of partial albinism.

The proximal and distal pigmentation of different golden scalp hairs of about the same age (case 2) is of interest. It suggests that local fluctuations in pigmentary activity are still occurring.

A further point of interest is the presence of lentigines: Brown[7] has stated that these pigmented spots may be related to infection or to hypoadrenia. There was no evidence of either factor in these cases. The occurrence of lentigines in albinos has often been looked on as an attempted defense against sunlight on the part of a vulnerable skin. Both of these patients, however had cutaneous pigment which was ample to prevent actinic trauma, and one must conclude that lentigines are an integral part of the albinotic syndrome.

SUMMARY

Two Negroes with partial albinism, a red and a yellow Negro, were encountered, both of whom showed nystagmus of the congenital type.

In the case of the yellow Negro fluctuation in pigmentary activity of the hair follicles was inferred.

5. Wolfrum: Zur Anatomie des menschlichen Albinoauges, Arch. f. Ophth. **84**:401, 1913; cited by Meirowsky.[4]

6. Seefelder: Beiträge zur Histogenese und Histologie der Netzhaut des Pigmentepithels in des Sehnerven, Arch. f. Ophth. **73**:419, 1910; cited by Meirowsky.[4]

7. Brown, E. E.: Lentigines: Their Possible Significance, Arch. Dermat. & Syph. **47**:804 (June) 1943.

AGRANULOCYTOSIS FOLLOWING MAPHARSEN THERAPY

REPORT OF TWO CASES

LIEUTENANT COLONEL MILOSH KASICH
MEDICAL CORPS, ARMY OF THE UNITED STATES

Agranulocytosis following mapharsen therapy is sufficiently rare to make the following case reports of interest:

CASE 1.—A 19 year old Negro soldier was admitted to the station hospital, Fort Dix, N. J., on Dec. 16, 1943, complaining of sore throat, malaise, chills and fever, all of two days' duration. Five weeks prior to his admission the patient had had a sore throat, mucous patches and a maculopapular rash which were considered manifestations of secondary syphilis. The Wassermann reaction was 4 plus. He was given standard antisyphilitic therapy, consisting of two injections of mapharsen weekly, beginning with 0.03 Gm. and increasing to 0.06 Gm. per dose. The patient had received five intravenous injections of mapharsen totaling 0.28 Gm. and three intramuscular injections of bismuth subsalicylate in oil totaling 1 Gm. He had received the last injection of mapharsen on December 14, with no immediate reaction. A few hours later, however, he began to experience chilly sensations and felt feverish. The next day he was extremely weak. On admission to the hospital he was prostrated, and dehydrated; his temperature was 103 F., and his pulse rate was 106. The physical examination revealed nothing significant except a diffuse edema of the peritonsillar regions with superficial ulceration of the right pharyngeal area. The blood pressure measured 120 systolic and 80 diastolic. The leukocyte count at this time totaled 2,800 white blood cells, with 24 per cent polymorphonuclear leukocytes. The Kahn reaction was negative. The leukopenia together with the diminished number of granular cells suggested the possibility of agranulocytosis secondary to mapharsen therapy. The patient was given 4 Gm. of sulfadiazine initially and 2 Gm. every four hours thereafter. Treatment also included a transfusion of 500 cc. of citrated whole blood and injection of pentnucleotide, 10 cc. every four hours (40 cc. per day) given intramuscularly. To preserve the fluid balance, the patient received 4,000 cc. of 5 per cent dextrose in isotonic solution of sodium chloride. On December 17 the leukocyte count was 2,750; the differential smear revealed a complete absence of granulocytes. The temperature was 105.4 F. The prostration was intense; the edema of the throat had increased, and the patient had great difficulty in swallowing. The intravenous administration of fluids and the pentnucleotide and sulfadiazine therapy were continued; another transfusion of 175 cc. of citrated blood was given. The next day the patient acquired a cough and examination of the lungs showed diminution of breath sounds over the middle third of the left lung. A roentgenogram confirmed the presence of a pneumonic process involving the lower part of the upper lobe of the left lung. The temperature increased to 105.6 F., and the patient's condition became poor. The leukocyte count at this time was 2,000, with no polymorphonuclear cells. On December 19, three days after entry into the hospital, the peripheral blood was still free of granulocytes and the patient's condition was critical. He was again given 500 cc. of citrated whole blood; the administration of sulfadiazine and pentnucleotide was continued, and sufficient fluid was given intravenously to maintain a urinary output of 1,500 cc. daily. On December 20, the white blood cell count rose to 3,800 leukocytes, 1 per cent of which were polymorphonuclear. On December 21, the patient's general condition suddenly improved. The temperature became normal. Examination of the blood revealed 68 per cent of the leukocytes to be of the granular series. Use of sulfadiazine was discontinued at this time. The improvement continued during the next day, at which time the white blood cell count reached a level of 4,600, with 51 per cent polymorphonuclear leukocytes. The patient subsequently made an uneventful recovery. Altogether he received 67 Gm. of sulfadiazine, 240 cc. of pentnucleotide and four transfusions of citrated blood, totaling 1,475 cc. (table 1).

TABLE 1.—*Hematologic Data, Case 1*

Date	Red Blood Cells, Millions	Hemoglobin Content (Tallqvist), per Cent	White Blood Cells	Polymorphonuclear Leukocytes, per Cent	Lymphocytes, per Cent	Transfusions of Citrated Blood, Cc.	Pentnucleotide, Cc. Daily	Sulfadiazine, Gm. Daily
12/16	4.12	85	2,800	24	76	500	40	7
12/17	4.05	80	2,750	0	100	175	40	12
12/18	....	..	2,000	0	100	500	40	12
12/19	....	..	2,850	0	100	300	40	12
12/20	4.41	80	3,800	1	99	...	40	12
12/21	....	..	3,700	68	32	...	40	6
12/22	4.38	85	4,600	51	49	...	20	6
12/23	....	..	6,300	66	34	...	20	0
12/24	5.18	85	6,350	55	45	...	10	0
12/26	....	..	6,200	52	48	...	10	0
12/27	5.2	85	5,000	54	46	...	10	0
12/28	4.9	86	6,450	53	47	...	10	0

CASE 2.—A 34 year old Negro soldier was admitted to the station hospital, Fort Dix, N. J., on Dec. 13, 1943, with the following history: At 10 o'clock that morning he had received his fifth injection of mapharsen, and two hours later nausea, vomiting, headaches, chills and fever had developed. His previous history

was unimportant, except for the presence of syphilis, which had been discovered on routine hematologic examination at the time of his induction into the Army, seven weeks before his present illness. He did not recall having had any lesions and had never received any treatment for syphilis. Prior to his admission to the hospital he had received five injections totaling 0.27 Gm. of mapharsen, with no untoward reaction. He had also been given three intramuscular injections of bismuth subsalicylate in oil totaling 0.6 Gm.

The temperature on entry was 101 F. Physical examination revealed no abnormalities except for superficial ulceration of the gums. The blood pressure measured 125 systolic and 80 diastolic. A smear taken from the ulcerated area and stained with methylthionine chloride (methylene blue) showed on examination the usual flora. The Kahn reaction was positive. The patient received symptomatic treatment, and a potassium permanganate mouth wash was prescribed for the gingival lesions. A blood count was not made at this time. The patient's condition remained unchanged and on December 16, three days after his admission to the hospital, his blood count was 3,550,000 red blood cells with 80 per cent hemoglobin (Tallqvist) and 6,650 white blood cells, with 52 per cent polymorphonuclear leukocytes. On December 20, the patient appeared gravely ill and toxic and complained of difficulty in swallowing. The gums were grayish and studded with small superficial ulcers, and there was edema of the pharynx. The white blood cell count now measured 2,350 with only 4 per cent polymorphonuclear neutrophils. The leukopenia with great reduction in polymorphonuclear cells, fever, sore throat, ulcerated gums, toxemia and intense prostration in a patient who had been receiving mapharsen indicated a diagnosis of agranulocytosis secondary to arsenical treatment. Therapy included a transfusion of 250 cc. of citrated whole blood, pentnucleotide, given intramuscularly in 10 cc. doses four times daily, and sulfadiazine, 4 Gm. initially and 2 Gm. every four hours thereafter. Sufficient fluid was given intravenously to maintain a urinary output of at least 1,500 cc. per twenty-four hours. On December 22, nine days after his admission to the hospital, the patient's condition became worse. The temperature was 104.6 F. and the pulse rate 140. The ulcerated gums became distinctly necrotic in appearance, and the white blood cell count was 1,600, only 1 per cent of which was granular cells. The patient was given an additional 200 cc. of blood; the administration of pentnucleotide and sulfadiazine was continued. On December 23 his condition was critical. The temperature was 104 F., the pulse rate 140 and the white blood cell count 2,300, with a total absence of polymorphonuclear cells. A study of the sternal bone marrow showed a few granular cells, occasional myeloblasts and lymphocytes. The appearance of the marrow was one of definitely diminished granulocytic activity. The next day the patient was still gravely ill, and the same quantities of blood, pentnucleotide and sulfadiazine were given. On December 25 the white blood cell count had risen to 4,500, with 5 per cent polymorphonuclear neutrophils, and the patient's condition had improved slightly. On December 26 the granulocytes had again disappeared from the peripheral blood, but on the next day the patient showed a definite improvement, his white blood cell count rising to 4,100, with 18 per cent granular cells. From this time on, improvement was progressive, and the patient subsequently made an eventful recovery. During his illness he had received 104 Gm. of sulfadiazine, 330 cc. of pentnucleotide and six transfusions totaling 1,500 cc. of citrated whole blood (table 2).

TABLE 2.—*Hematologic Data, Case 2*

Date	Red Blood Cells, Millions	Hemoglobin Content (Tallqvist), per Cent	White Blood Cells	Polymorphonuclear Leukocytes, per Cent	Lymphocytes, per Cent	Transfusions of Citrated Blood, Cc.	Pentnucleotide, Cc. Daily	Sulfadiazine, Gm. Daily
12/16	3.55	80	6,650	52	48	...	0	0
12/20	3.53	80	2,350	4	93	...	10	0
12/21	....	..	1,800	4	96	250	40	14
12/22	....	..	1,600	1	99	250	40	12
12/23	3.79	75	2,300	0	100	250	40	12
12/24	4.12	80	2,000	0	100	250	0	12
12/25	4.19	80	4,700	5	95	250	0	12
12/26	4.05	80	2,800	1	99	250	40	12
12/27	4.23	80	4,100	18	82	...	40	12
12/28	....	80	3,400	19	81	250	40	12
12/29	....	..	4,350	56	44	...	20	6
12/30	....	..	5,250	59	41	...	20	4
12/31	....	..	5,600	60	40	0	20	4
1/ 1	4.18	85	4,600	59	41	...	20	4
1/ 2	....	..	5,450	54	46	...	20	4
1/ 3	....	..	6,000	60	40	...	10	4
1/ 4	....	..	7,250	72	28	...	10	4

COMMENT

Although agranulocytosis, aplastic anemia and thrombocytopenic purpura following mapharsen therapy have been reported in the literature,[1] these reactions are rare.[2] Injury to the bone marrow from trivalent arsenicals in Negroes, moreover, is said to be extremely uncommon.[3]

1. Kirkham, D., and Perlmutter, M.: Fatal Aplastic Anemia Following Use of Mapharsen: Report of a Case, Arch. Dermat. & Syph. **43**:111 (Jan.) 1941. Cresswell, G. W., and Roth, G. G.: Fatality from Mapharsen Treatment of Syphilis, M. Ann. District of Columbia **10**:230, 1941. Rangiah, P. N.: Death Following Mapharsen Therapy, Correspondence, J. A. M. A. **115**:319 (July 27) 1940.

2. Levin, E. A., and Keddie, F.: Toxic Effects Following Use of Mapharsen, J. A. M. A. **118**:368 (Jan. 31) 1942.

3. Irgang, S.: Gastric Intolerance Accompanying Arsphenamine Therapy, Am. J. Syph., Gonor. & Ven. Dis. **25**:241, 1939.

In Nelson's [4] series of 4,066 patients who had received 15,607 injections of mapharsen, only 2 instances of blood dyscrasia occurred. These figures are representative of those reported by other observers.[2]

The agranulocytosis in the cases herein reported can be ascribed to the mapharsen with a fair degree of certainty. Idiopathic agranulocytosis has been described, but is unusual; indeed, some investigators believe that it occurs rarely.[5] My patients had taken no other drug known to cause granulocytopenia. The length of time required for the damage to the bone marrow to become evident varies. In two series of 41 patients reported on by McCarthy and Wilson [6] and Loveman,[7] blood dyscrasia following the injection of trivalent arsenicals developed in 13 cases after five to twelve doses and in 27 cases after fourteen to forty doses and in 1 case after fifty doses. In this same group 10 patients showed evidence of damage to bone marrow in one day or less; 26 in one to thirty days and 5 in over thirty days. My patients were given five doses of mapharsen in thirteen and twenty-one days and received 0.28 and 0.27 Gm. respectively.

The mechanism by which drugs produce agranulocytosis is unknown. Individual susceptibility appears to be the most important factor. Pepper's [8] suggestion that the disease might be "allergic" apparently has been confirmed by some observers [9] who were able to reproduce granulocytopenia on readministration of aminopyrine to persons who had recovered from the disease after previous use of this drug. Most investigators, however, have been unable to confirm the allergic nature of the agranulocytosis. Whether the process is allergic or toxic, it is generally agreed that the drugs acting on the bone marrow produce an "arrest" of maturation of the precursors of the granulocytes, the "arrest" occurring at the myeloblastic level.[10] Biopsy of sternal marrow reveals a characteristic deficiency in the maturing myelocytes. While this disturbance of maturation is the primary factor, an abnormal peripheral disturbance of the polymorphonuclear cells or segregation of the cells such as would occur if they should adhere to the capillary endothelium must also be assumed, for only in this way can their rapid disappearance from the blood stream be explained.[11]

The treatment of this disease has been varied and the results unpredictable, for few observers have had a sufficient number of cases to give any one method a thorough trial. Reznikoff [12] pessimistically stated that aside from prophylaxis treatment is unsatisfactory. Yellow bone marrow extract, roentgen therapy, injections of liver extract, leukocyte cream or derivatives of nucleic acid (adenine sulfate and pentnucleotide) and blood transfusions in his opinion have slight if any value, and there is no good evidence that any patients have ever recovered through their use.

The high mortality of this disease results not from the absence of granulocytes in the circulating blood but from the inevitable sepsis which overwhelms the patient when the body loses this protective mechanism. That the septicemia is usually secondary to the agranulocytosis is now firmly established. The disappearance of granular cells has been ascribed to the septicemia itself by some observers. However, in leukopenia resulting from septicemia it is extremely rare to find a total absence of granular cells. A finding of 10 per cent or more is usual. Since the septicemia follows the agranulocytosis, it seems logical, as Dameshek and Wolfson [13] suggested, to place the emphasis in treatment on control of the sepsis after use of the offending drug has been discontinued. These observers have successfully treated 2 patients with sulfadiazine, basing their therapy on the belief that if the septicemia can be kept under control the bone marrow will have time to recover and resume normal function. There has been an

4. Nelson, R.: Personal communication to the author.

5. Jackson, H., Jr.: Medical Progress: Leukopenia; Agranulocytosis, New England J. Med. **225**:978, 1941.

6. McCarthy, F. P., and Wilson, R., Jr.: The Blood Dyscrasias Following the Arsphenamines, J. A. M. A. **99**:1557 (Nov. 5) 1932.

7. Loveman, A. B.: Toxic Agranulocytopenia, Purpura Hemorrhagica, and Aplastic Anemia Following the Use of Arsphenamines, Ann. Int. Med. **5**:1238, 1932.

8. Pepper, O. H. P.: Leukopenia—A Review, with Special Reference to Agranulocytic Angina, California & West. Med. **35**:82 and 173, 1931; History of Agranulocytic Angina, J. A. M. A. **97**:1100 (Oct. 10) 1931.

9. Madison, F. W., and Squier, T. L.: The Etiology of Primary Granulocytopenia (Agranulocytic Angina), J. A. M. A. **102**:755 (March 10) 1934.

10. Fitzhugh, T., and Krumbhaar, E. B.: Myeloid Cell Hyperplasia of Bone Marrow in Agranulocytic Angina, Am. J. M. Sc. **193**:104, 1932.

11. Rohr, K.: Der heutige Stand der Agranulozytoseforschung, Helvet. med. acta **6**:611, 1939.

12. Reznikoff, P.: Agranulocytosis and Leukopenia, J. A. M. A. **115**:128 (July 13) 1940.

13. Dameshek, W., and Wolfson, L. E.: A Preliminary Report on the Treatment of Agranulocytosis with Sulfathiazole, Am. J. M. Sc. **203**:819, 1942.

understandable hesitancy to administer sulfonamide compounds to patients with agranulocytosis, since these drugs have been known to cause it.[14] However, there appears to be a specificity in the sensitivity of the bone marrow to drugs. Thus, a bone marrow adversely influenced by one drug will not necessarily be affected by another, even though this compound may have produced toxic effects in other cases. This fact is well illustrated by reports of patients who tolerated mapharsen although neoarsphenamine previously had produced a depression of activity of the bone marrow.[15]

14. Levin, M., and Bethell, F. H.: Fatal Granulocytopenia Developing During the Administration of Sulfadiazine, Univ. Hosp. Bull., Ann Arbor **8**:30, 1942. Carley, P. S., and Reid, P. E.: Granulocytopenia Resulting from Sulfonamide Therapy: Case Report, U. S. Nav. M. Bull. **40**:165, 1942.

SUMMARY AND CONCLUSION

This report adds 2 additional cases of agranulocytosis attributable to mapharsen therapy to those already reported.

Although agranulocytosis appears to be an infrequent complication of mapharsen therapy, frequent leukocyte counts should be made on all patients receiving this drug to anticipate the possibility of its occurrence and institute the best available methods of treatment.

15. Goldberg, M.: Mapharsen as a Substitute for Neoarsphenamine in Agranulocytic Angina Following Neoarsphenamine Therapy in a Pregnant Woman, Am. J. Syph., Gonor. & Ven. Dis. **23**:79, 1939.

POISON IVY SMOKE

EXPERIMENTS DEMONSTRATING THAT POISON IVY SMOKE IS NOT A CAUSE OF CLINICAL IVY DERMATITIS

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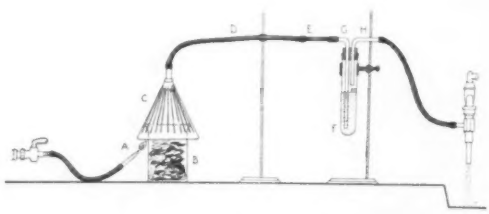
Only one investigation has recently been made, using a single ivy-sensitive subject, in an attempt to disprove the popular belief that smoke from the burning poison ivy plant contains the dermatitis-producing factor.[1] The purpose of this communication is to report the results of 2 different experiments which conclusively demonstrated that the smoke of the Rhus group of poisonous plants is not per se a cause of clinical ivy dermatitis.

The dermatitis-producing fraction of poison ivy is readily soluble in acetone and ether.[2] With the assistance of Dr. Vern Rhoer, of the department of biochemistry of the Southwestern Medical College, a simple method was devised for passing smoke through acetone by means of suction. If the allergenic fraction is present in the smoke, it will be removed by the solvent acetone. Contact tests on ivy-sensitive subjects



Apparatus for extraction of poison ivy smoke.

with a few drops of the acetone-smoke extract, concentrated by evaporation, would then indicate whether the dermatitis-producing factor is present in the smoke.

A mixture of dried leaves, stems and branches of Rhus toxicodendron, Rhus quercifolia and Rhus diversiloba weighing 50 Gm. was burned as a source of smoke for each individual test. A rubber tube with a pointed glass tip was employed as a means of conveying gas to ignite the ivy (the figure). A portion of the 50 Gm. of material was placed in an 800 cc. beaker (*B*) and was ignited by the burning gas jet (*A*). As soon as the leaves commenced to burn, a funnel (*C*) 17 cm. in diameter was placed over the top of the beaker. Numerous clouds of smoke followed. Negative pressure created by running tap water through a suction pump attached to the faucet was used to pull the accumulating smoke through the rubber hose (*D*) into a 75 cc. test tube (*F*) which contained 35 cc. of acetone. The smoke was carried into the test tube through an L-shaped piece of glass tubing (*G*) and escaped into the acetone and was drawn to the outside again through another rubber tube (*H*).

It was necessary to ignite the ivy at repeated intervals. New portions of the original 50 Gm. mass were added to the beaker as soon as the fire completely destroyed the portion being burned. From thirty to forty-five minutes was required to burn the 50 Gm. of the plant.

The smoke discolored the clear acetone a light brownish or amber color, and numerous small particles of soot and leaves were noted in suspension. This acetone extract of the poison ivy smoke produced definitely positive reactions on ivy-sensitive persons. When the experiment was repeated a second and a third time, the resulting contact test likewise elicited positive reactions.

The particles of soot and leaves that were observed in suspension were thought to be in sufficient quantity to account for the positive contact reactions. A piece of glass tubing (*E*) loosely filled with absorbent cotton was introduced into the apparatus to filter these fragments from the smoke.

The procedure of burning 50 Gm. of ivy leaves and extracting the filtered smoke by passing it through acetone was repeated three times. The cotton in the glass tube was observed carefully, and as soon as it became discolored it was replaced. The color of the acetone was noted to change from clear to a light amber. The solution possessed a strong odor of smoke, but few particles were detected. The quantity of acetone was reduced during the procedure from 35 to 18 cc. By open evaporation this volume was further reduced to 2 cc., to be used for patch testing.

Ten persons who had experienced repeated attacks of clinical ivy dermatitis and recently had reacted positively to patch tests with poison ivy extract were selected to determine whether or not the concentrated acetone extract of the smoke contained the dermatitis-producing factor. All

1. Shelmire, B.: Nonallergic Nature of Poison Ivy Smoke, Arch. Dermat. & Syph. **43**:384 (Feb.) 1941.

2. Howell, J. B.: Solubility of the Dermatitis Producing Fraction of Poison Ivy, Arch. Dermat. & Syph. **44**:665 (Oct.) 1941.

ntact tests elicited negative reactions in these
f subjects, the three different specimens of the
etone extracts of smoke obtained from the last
ree tests in which the soot and particles were
tered from the smoke being used.

Unfiltered smoke from the end of the tube
D) was next allowed to contact continuously an
ea approximately 3 inches (7.5 cm.) in diame-
r on the forearms of 2 ivy-sensitive subjects for
o minutes. A dermatitis failed to follow this
posure to smoke.

According to McNair,[3] ivy poisoning without
ntact with the poison ivy plant may occur from
e smoke of the burning shrub. Von Adelung,[4]
perimenting with poison ivy smoke in 1912,
aced a small quantity of poison ivy leaves in
glass combustion tube. The tube was heated
til the leaves began to smoke. The smoke was
en blown against the skin of a susceptible
rson. A dermatitis followed. The experiment
as repeated with the addition of cotton plugs
each end of the tube. A dermatitis did not
sue.

After repeating von Adelung's[4] experiment,
cNair concluded that the smoke is not poison-
s when filtered through glass wool at a high
mperature. At the time of McNair's experi-
ents with poison ivy smoke, little was known
out allergic contact type of dermatitis. His
nclusions cannot be evaluated, since it is diffi-
lt to determine whether or not he was dealing
th persons clinically sensitive to poison ivy.
cNair used the milky sap of the plant, which
a primary irritant, as a test for sensitivity to
ison ivy.

The second experiment was a repetition of the
ocedure originally carried out by Dr. Bedford
elmire[2] and repeated under his supervision.

Ten medical students were selected for this test. ese men were chosen because they had experienced merous previous attacks of ivy dermatitis and were nsidered to have a higher than average degree of nsitivity to the plant. It was only after persuasion at 4 of the group submitted to the experiment, since y were convinced that severe dermatitis venenata uld ensue.

The volunteers removed all of their clothing except eir trousers, which were rolled above the knees. They re confined in a closed garage room which measured proximately 10 by 12 feet (3 by 3.7 meters). About pounds (13.6 Kg.) of a mixture of dried leaves, roots d branches of Rhus toxicodendron, Rhus quercifolia d Rhus diversiloba was placed in an open container and slowly burned. At intervals more leaves were added to the burning mass. This created innumerable clouds of grayish white smoke containing soot and small particles of charred leaves. Each student bathed his arms, face, chest and back in the smoke for twenty minutes except for intervals of a few seconds, during which time short trips were made to the outside for air.

In 7 subjects no evidence of dermatitis developed. Three men purposely held both forearms 12 to 18 inches (30 to 45 cm.) above the burning leaves for approximately five minutes. The heat at that distance made it necessary to withdraw the forearms frequently. A mild dermatitis of both forearms followed in 2 subjects, and a dermatitis of only one forearm developed in the third. The eruptions appeared twelve to twenty-four hours after exposure and remained visible for approximately seventy-two hours. The face, neck, trunk and upper part of the arms of these volunteers, although exposed to large volumes of smoke while the forearms were in close proximity to the burning leaves, did not acquire a dermatitis.

COMMENT

The small particles of poison ivy leaves, soot and charred matter carried by the smoke, with the aid of the suction, contained enough ivy oleoresin when dissolved by the acetone to produce positive contact reactions on ivy-sensitive persons. Elimination of these contaminants by a replaceable cotton filter demonstrated that smoke does not contain a dermatitis-producing factor. The exposure to smoke in the groups of medical students was more massive than any individual would ever actually encounter from a brush fire. No evidence of ivy dermatitis appeared in 7 students who were exposed only to the smoke. Three students acquired a mild dermatitis only on the forearms, held directly over the flame of the burning ivy, although the remainder of the body was bathed in volumes of ivy smoke.

It may be speculated that the dermatitis of the forearms of the 3 men was due to heat or that a vapor containing a small quantity of the dermatitis-producing factor was present at a distance of 12 to 18 inches (30 to 45 cm.) above the burning leaves. No eruption followed exposure of the forearms 2 feet (60 cm.) above the burning leaves and brush. This is in agreement with the experience of Shelmire.[1]

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3. McNair, J. B.: Rhus Dermatitis, ed. 1, Chicago, iversity of Chicago Press, 1923, pp. 72-73.
4. Cited by McNair.[3]

JOHN GORRIE, M.D., AND AN EARLY CASE OF KELOID

IRVING S. CUTTER, M.D.

CHICAGO

The chance perusal of one of the early volumes of the *Transylvania Journal of Medicine* revealed what is probably the first American description of keloid. If so, the author, Dr. John Gorrie, has an additional claim to fame. A pioneer in the manufacture of artificial ice, he devised an apparatus which, although not developed on a commercial scale, was experimentally successful. While many names are associated with the birth of refrigeration, Gorrie was years ahead of others in the air conditioning of sickrooms, the insulation of homes and the freezing of water for domestic and sanitary use.

ART. IV.—*Observations on a case of Disposition to form Remarkably large Cicatrices.* By JOHN GORRIE M. D. of Abbeville, South Carolina.

MORBID affections of the skin have been in all ages, from the disgust and dread with which some of their species have been viewed, subjects of interest to mankind; and they would seem, from a variety of causes, destined always to continue objects of embarrassment to the medical practitioner. The researches of science, and the results of practical observation fail alike to reduce to order the confusion in which the characteristic distinctions of a considerable number of those complaints are involved. Presenting under the operations of different habits, climates and other occurrences, a greater variety in appearance than any other class of diseases, they have in consequence, produced, among writers, more conflicting views of their character—mere individuals, existing in different countries, of the same form of complaint have been classed as distinct disorders, while maladies possessing no common connexion have been considered of the same or a similar nature. This discrepance of opinion is scarcely less apparent in the descriptions of strictly endemial complaints; and in parts of the world in

Fig. 1.—Page 1 of Gorrie's description of Keloid. (From Gorrie, J.: Transylv. J. Med. **3**:384, 1830.)

In the course of his medical practice at Abbeville, S. C., one of his patients presented a number of peculiar growths which seemed to proceed from the epidermis and which he termed "large cicatrices." His paper, "Observations on a case of Disposition to form Remarkably large Cicatrices," was published in the August 1830 number of the *Transylvania Journal of Medicine* (fig. 1). In this illuminating report, Gorrie described keloid and made two original observations: first, the susceptibility of Negroes and, second, that an injury such as "the prick of a pin, the sting of a hornet, the scratch of a thorn or a trifling cut or burn" usually precedes the development of the overgrowth.

Concerning the pathology, Gorrie set forth a modern point of view. He remarked that he was convinced that the lesions are "exuberant extensions of the healing process by which a cicatrix is formed." He continued, "There is an evident disposition in the system to extend the cutaneous structure beyond the healthy limits assigned to that organ." He then theorized that an increase of fibrin in the circulation is probably responsible.[1] One other observation, namely, that the malady rarely presents itself before puberty, is left unexplained except on this postulate. Concerning treatment, Gorrie failed to agree with his local colleagues. He found that blisters and plasters, as well as internal remedies such as mercury and arsenic, either had no effect or made the condition worse. As he put it, "escharotics tend to increase it."

Dermatologists are familiar with the contributions of Jean-Louis Alibert (1766-1837) to their specialty. Our physician-poet Oliver Wendell Holmes listened to his lectures in Paris and described him as a "jolly old party, a good deal of a dandy." Alibert first observed keloid in 1810, terming the condition *cancroïde*. Later, in 1816, he proposed the new designation and included in his paper a more accurate description.[2] Five cases were listed. In this discussion he remarked that keloid forms an intermediate stage between herpes and cancer. Publishing his report fourteen years before Gorrie's description, he failed to give a single hint concerning causation. He did point out, however, that subsequent to the use of silver nitrate and other caustics "the malady soon reappears, oft'times in aggravated form." He deplored the

1. In the light of the recent paper by W. Marshall and S. Rosenthal (Pathogenesis and Experimental Therapy of Keloid and Similar Neoplasms in Relation to Tissue Fluid Disturbances, Am. J. Surg. **62**:348 [Dec.] 1943) this suggestion may not be so far afield.

2. Alibert, J.-L.: J. univ. d. sc. med., Paris **2**:207-216, 1816.

fact that internal remedies, as well as external applications, had been without avail.

Albert failed to discuss the fundamental pathologic changes. He did remark, however, that "the tumors show fibrous tissue." But they are not, as he insisted "like the glandular substance of a breast." Evidently it did not occur to him that trauma played an important role. His long dissertation dealt largely with symptoms and the general appearance of the lesions. His case 2 may not have been a case of keloid at all, as he stated that the small tumor progressed for a time but later diminished. It is doubtful if the lesion in case 5 was a keloid.

A word about John Gorrie and his medical career may not be out of place. Most biographers agree that he was born in Charleston, S. C., Oct. 3, 1803. Thereafter, data concerning his medical education and attainments are either incorrect or omitted from all published biographies which I have been able to find. The statement that he graduated from the College of Physicians and Surgeons, New York city, about 1833, is erroneous. This arose from a remark made by Asa Gray to one of Gorrie's fellow townsmen, a brother practitioner, the eminent physician-botanist Arthur Wentworth Chapman (1809-1899).[3] Gray related that while an assistant in the chemical laboratory of the College of Physicians and Surgeons, New York city, in 1833 he recalled Gorrie as a superior student. The fact is that Gorrie graduated from Fairfield Medical College on Jan. 31, 1827. This school was under the jurisdiction of the Board of Regents of the State of New York, and its official designation was "The College of Physicians and Surgeons of the Western District of New York, Fairfield, Herkimer County." His name appears in the list of graduates of that year (fig. 2). There is included also the title of his thesis, "Neuralgia." This essay was published in the autumn number of the *New York Medical and Physical Journal* for 1828, pages 325-343. It is a scholarly production. Obviously he had access to the accepted authorities of the day. In addition, he made numerous unique observations. The paragraphs on diagnosis are well worth reading today, as he differentiated the malady from hemicrania, toothache and abscess of the antrum. Another paper from Gorrie's pen, "A fatal case of delirium tremens," appeared in the *New York Medical and Physical Journal* **1**: 312-317, 1829.

3. Chapman received an honorary M.D. from the University of Louisville with the class of 1846. This fact has not been reported hitherto.

Asa Gray's association with Gorrie no doubt occurred at Fairfield, where Gray graduated Jan. 5, 1831. In one of his letters Gray wrote, "I entered upon the study of medicine in the autumn of 1826, beginning with the session of 1826-27 in the Medical College (of the Western District), then a flourishing country medical school at Fairfield." Gorrie was in the senior class at the time, and there Gray must have made his acquaintance.

Gorrie's interest in mechanical refrigeration arose from his desire to ameliorate the sufferings of victims of malaria. He reasoned that the ravages of the disease would be lessened if

College of Physicians and Surgeons of the Western District.—The Regents of the University on the 31st of January, 1827, conferred the degree of Doctor of Medicine on the following gentlemen, recommended by the Trustees of the above College, after having passed the required examinations, and read and defended Theses, as follows:

1. Walker L. Bean, of South Carolina, on the Functions and Sympathies of the Liver.
2. Chauncey D. Bull, of Saratoga county, New-York, on the Effects of Light.
3. Archibald Catlin, of Herkimer county, on Hypochondriasis.
4. Amherst Childs, jun. of Seneca county, on Antimony.
5. Meriwether L. Cobbs, of Virginia, on Chronic Hepatitis.
6. William J. Delavan, of Seneca county, on Croup.
7. Jesse Day, of Monroe county, on Syphilis.
8. Stephen Gay, of Vermont, on Dysentery.
9. John Gorrie, of South Carolina, on Neuralgia.
10. Charles C. Haddock, of Erie county, on Cholera.
11. Jacob Jimeson, of Erie county, on the Customs, Habits, and Diseases of the Seneca tribe of Indians.
12. Moses Johnson, of Herkimer county, on the Epidemic Fever of 1826, as it prevailed in Salisbury and Fairfield, Herkimer county.
13. James Lawrence, of Saratoga county, on Phthisis Pulmonalis.
14. Dyer Loomis, of Montgomery county, on the Effects of Difficult Dentition.
15. Finlay M'Martin, of Saratoga county, on Uterine Hæmorrhage.
16. Peter P. Murphy, of Montgomery county, on the Influence of the Mind on the Body.
17. William W. Nugent, of Albany county, on Croup.
18. Noyes Palmer, of Onondago county, on the Phenomena and Treatment of Old Age.

Fig. 2.—List of graduates of the College of Physicians and Surgeons of the Western District of the State of New York, Fairfield, for 1827. (From New York M. & Phys. J. **6**:158, 1827.)

some means could be found to reduce the fever. In order better to inform the public concerning the nature of this malady, he wrote a series of articles which were published in the press of Apalachicola, Fla., to which community he had removed in 1833. These are well known to his biographers. In addition, he prepared two articles on malaria which appeared in the *New Orleans Medical and Surgical Journal* (**11**: [March and May] 1855). He set forth therein the application which he proposed to make of air conditioning in the control of fever. The second article also called attention to the importance of insulation in the construction of human habitations.

The later years of his life, which ended June 16, 1855, were devoted to perfecting his ice machine, and he apparently journeyed to numerous points seeking financial help as well as scientific data. On one occasion he stated that he performed some experiments in New York city in the winter of 1852-1853. In tracing the relationship between physical forces, he found that a disk of ice at a temperature a few degrees above zero (F.) could be excited by a catskin so as to emit sparks.

There is a monument to Dr. John Gorrie in Apalachicola, Fla., and air-conditioned Statuary Hall, Washington, D. C., houses his effigy. He is a worthy representative of his state and his nation in the Hall of Fame.

The purpose of this article is to call attention to what may be the first American description of keloid and, second, to correct errors which have crept into the biographic sketches of this distinguished Southern physician.[4]

303 East Superior Street.

4. An excellent bibliography accompanies the article on Gorrie by H. M. Taylor (Taylor, H. M.: John Gorrie: Physician, Scientist, Inventor, South. M. J. 28: 1075 [Dec.] 1935) of Jacksonville, Fla.

EFFECT OF GRENZ RAYS ON LEPROUS INFILTRATIONS

REPORT OF AN ATTEMPT TO INFLUENCE LEPROUS INFILTRATIONS BY ROENTGEN RAYS OF LONG WAVELENGTH

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Since there exists no specific therapy for leprosy and the results of general therapeutic measures are poor, every new case encountered makes one wish that one were able at least to influence the lesions locally. This is all the more important (1) when the aspect is particularly repulsive; (2) when the lesions tend to grow rapidly; (3) when they may cause harm to neighboring organs, and (4) when they hamper the mobility of joints.

When roentgen and radium rays were first tried in the treatment of leprous nodules and infiltrations, the results were rather favorable; but soon severe damage to the surrounding skin and underlying organs was also reported. Since I knew that grenz rays were far less dangerous in this respect, it seemed worth while to try them in treatment of leprous infiltrations and to watch the response to this type of rays, all the more as on perusal of the literature at my disposal and in a search through the *Quarterly Cumulative Index Medicus* no reference to experiments of this kind could be discovered.

In view of the superficial action of the rays employed, no satisfactory results could be expected from the exposure of large tumors; and so only superficial as well as deeper infiltrations of the skin were chosen for these studies. During the experiments some interesting reactions were observed which made it appear worth while to publish the preliminary results.

Case 1.—The patient, aged 79, was born in Lithuania and had lived in the United States for forty years before he came to Palestine, thirteen years ago. Four years before he was seen, leprosy of the mixed type was diagnosed for the first time. The patient then presented a facies leontina and also had scattered infiltrations on his extremities. On the mucous membrane of the nose and in the nodules Hansen bacilli could be identified. For two years he was treated with preparations of chaulmoogra oil and with trimethyldioxyoxotritan (rubrophren) and bismuth preparations but with no appreciable result.

To ascertain the effect of the rays on the leprous tissue as well as on the bacteria nine selected areas of skin were exposed to varying doses and qualities of rays. For control, one area of normal skin was included. In all instances bacteriologic examinations were regularly made. Dosage and radiation factors are given in the descriptions of the individual areas. The maximum voltage was between 6 and 14 kilovolts.

Area 1.—This area consisted of an infiltration on the left arm. On May 15, 1939 the area was irradiated, the following technical factors being employed: 1,000 r; skin-focus distance 10 cm.; 10 milliamperes; 170 volts, which is equivalent to a half value layer of 0.021 mm. of aluminum; 375 r per minute.[1] Violent erythema appeared after two weeks. On May 31 Hansen bacilli were identified in the area. On July 3, August 1 and September 27 a dose of 1,000 r was given—a total dose of 4,000 r. After each exposure the usual waves of erythema were observed to appear and disappear, with subsequent pigmentation. On September 25 the infiltration had disappeared but Hansen bacilli were still present.

On May 23, 1940 it was observed that all over the patient's body numerous erythematous patches and flat infiltrations had appeared, the area previously irradiated, however, being spared. The advance of the infiltration had been stopped abruptly at the border of the treated area. Hansen bacilli were found in the treated area as well as in the surrounding skin.

In February 1942 it was found that there had been no recurrence of infiltration in the treated area.

Area 2.—This was a large infiltration of angular outline on the distal part of the arm. The total dose of rays applied was 7,000 r, single doses being 1,000 to 2,000 r. The radiation factors were as for area 1, treatments being given at intervals of four to six weeks. After four months the infiltration had disappeared, while bacilli were still found in the area.

In February 1942 there had been no recurrence in the treated area, while in the surrounding skin fresh infiltrations had developed.

Area 3.—This area consisted of an infiltration on the left forearm. The total dose applied was 3,000 r, the single doses being 1,000 r each. The radiation factors were as for the other areas. The response recorded was the same as that of area 1.

Area 4.—This was an infiltration of the right arm. The total dose given was 600 r (two doses of 300 r each) with rays of soft quality. The infiltration remained unchanged.

Area 5.—An infiltration of the right forearm received a total dose of 2,000 r (two doses of 1,000 r each) with the following technical factors: skin-focus distance 15 cm.; 15 milliamperes; 210 volts, which is equivalent to a half value layer of 0.028 mm. of aluminum; 400 r per minute.[2] Treatments were given at an interval of be-

From the Dermatologic Department of the Rothschild-Hadassah University Hospital, Director, Dr. A. Dostrovsky.

1. Hereafter grenz rays of this type will be referred to as of soft quality.

2. Rays delivered with these factors will hereafter be referred to as of medium hard quality.

tween four and six weeks. Six months later the infiltration had disappeared but bacilli were still found in the area. A follow-up examination after two and three-fourths years showed that no fresh infiltrations had formed in the irradiated area.

Area 6.—This area was an infiltration of the left forearm. It was given a single dose of 2,000 r, delivered with the following technical factors: skin-focus distance 10 cm.; 15 milliamperes; 210 volts filtered through 0.01 mm. of cellophane, equivalent to a half value layer of 0.033 mm. of aluminum; 666 r per minute.[3] The response was the same as that recorded for area 5.

Area 7.—An infiltration of the right arm was given a single dose of 5,000 r of rays of medium hard quality. After two months violent erythema occurred with erosion of the skin, healing with atrophy. Hansen bacilli were still found. After two and three-fourths years the infiltration had disappeared and there were atrophy, telangiectases and pigmentation as well as areas of depigmentation. New infiltrations, which had developed in the meantime, had spared the treated area.

Area 8.—Clinically normal skin of the right arm was given a dose of 1,000 r of rays of medium hard quality. Bacilli were found in the area prior to and six months after treatment.

Area 9.—An area of leprous depigmentation (anesthetic) was chosen as a suitable object for the study of the effect of the rays on a depigmented area. At the same time, for control, part of the surrounding leprous infiltration was likewise exposed to the rays. On Aug. 3, 1939 a dose of 1,000 r of rays of medium hard quality was given. The response is shown in the following tabulation:

Date	Surrounding Leprous Infiltration	Depigmented Anesthetic Area
Aug. 14	Slight swelling; slight pigmentation	Scarcely recognizable redness; no pigmentation
Sept. 7	Dark pigmentation	Slight pigmentation
Sept. 27	Dark pigmentation	Dark pigmentation
Dec. 21	Dark pigmentation	Pigmentation has again disappeared.

It is seen from the tabulation that the depigmented anesthetic area acquired pigmentation more slowly than the rest of the skin and lost it more rapidly.

CASE 2.—The patient was 39 years old, was born in Palestine and lived in Tiberias. For five years he had been suffering from the mixed type of leprosy. Hansen bacilli were found on the mucous membrane of the nose and in cutaneous lesions. The Wassermann and Kahn reactions were negative. Therapy had included use of preparations of chaulmoogra oil and carbon dioxide. The experimental setup was similar to that employed in case 1. Nine areas were selected for irradiation. Bacteriologic examinations were made prior to and after treatment. All the lesions were on the patient's back.

Area 1.—An infiltration on the back was given a total dose of 6,000 r (single doses, 1,000 to 2,000 r) of rays of soft quality.

After nine months the infiltration had disappeared, but an eruption of new lesions all over the body accompanied with a rise of temperature was noted. The new infiltrations, covering almost the entire skin of the back, stopped abruptly in a curved line at the border of the previously treated area.

After one and one-half years, no recurrence had developed and the area showed patches of hyperpigmentation as well as of depigmentation.

Area 2.—The doses were the same as those used for area 1, and the rays were of medium hard quality. The response was the same as that recorded for area 1.

Area 3.—This area was given a dose of 1,000 r [illegible] hard quality rays, combined with carbon dioxide [illegible] ment. The results were dubious and are therefore [illegible] given in detail.

Area 4.—The total dose applied was 6,000 r (sing[illegible] doses 300 r) of rays of hard quality. The interv[illegible] were from one to three days. After the lapse of [illegible] months the infiltration had disappeared. Since, ho[illegible] ever, owing to the great number of exposures, the edg[illegible] were uneven, at some points fresh leprous tissue [illegible] advanced into the treated area. During one and [illegible] half years no recurrence developed in the area.

Area 5.—The total dose applied to this area was 7,0[illegible] r in single doses of 2,000 to 3,000 r of rays of medi[illegible] hard quality.

Area 6.—This area was given a total dose of 8,00[illegible] (single doses 4,000 r) of medium hard rays.

Area 7.—This area received 6,000 r single doses 2,0[illegible] r of hard rays.

Areas 5, 6 and 7 showed responses similar to th[illegible] of area 1.

Areas 8 and 9.—These areas, consisting of clinica[illegible] normal skin, were given exposures of 800 to 1,50[illegible] respectively of rays of hard quality. The infiltrati[illegible] which developed later did not stop at the border of t[illegible] treated area. Bacteriologic examinations prior to a[illegible] after treatment yielded positive results.

COMMENT

In 2 patients both presenting the mixed ty[illegible] of leprosy, a number of cutaneous infiltration[illegible] were exposed to the action of grenz rays unde[illegible] varying conditions. The results could be fol[illegible] lowed up over periods of from one and one-hal[illegible] to two and three-fourths years. The area[illegible] treated consisted in erythema, slight as well a[illegible] decided infiltration, depigmentation and, for th[illegible] purpose of control, clinically normal skin. Th[illegible] total doses given were between 600 and 7,000 r[illegible] with maximum voltage varying between 6 an[illegible] 14 kilovolts, which is equivalent to half valu[illegible] layers of 0.021 and 0.033 mm. of aluminum[illegible] The treatment consisted in large as well a[illegible] smaller fractional applications distributed ove[illegible] more or less lengthy periods.

It was seen that on exposure to more than 2,000 r the infiltrations would start to disappear. Smaller doses were ineffective. Proportionate to the thickness of the infiltrations, totals up to 8,000 r were applied. After between four months and one year, the areas exposed to radiation were free from symptoms clinically. There is therefore no doubt that a local effect similar to that of carbon dioxide, on leprous infiltration is possible by means of grenz rays.

A characteristic reaction of the areas of treated skin to fresh eruptions of leprous lesions on the body was noted. In case 1 six months and in case 2 nine months after the treatment had been started new lesions appeared on the patients' bodies. In both cases almost all the areas which had received radiation treatment were

3. Rays delivered with these factors will hereafter be referred to as of hard quality.

ared and the advance of the process abruptly alted at the border of the treated areas. Biopsy ecimens taken from one of the treated areas the time when the new eruptions appeared for radiation treatment as well as the surrounding infiltration and submitted to Professor Franco, director of the pathologic institute for study. His reports was as follows:

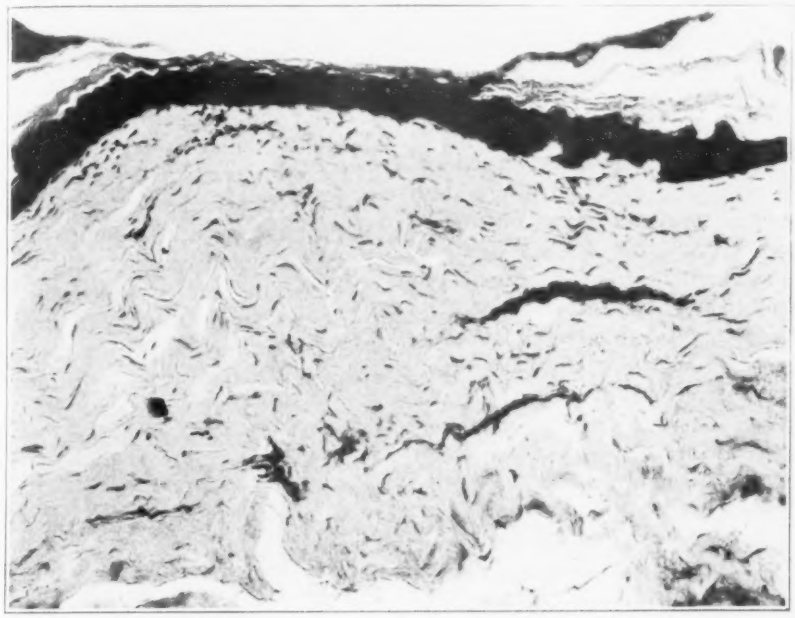

Fig. 1.—Section from a biopsy specimen from area 2, case 2, one-half year after the first exposure to grenz ra Note the slight cellular infiltration and the isolated Hansen bacilli. × 150; green filter.

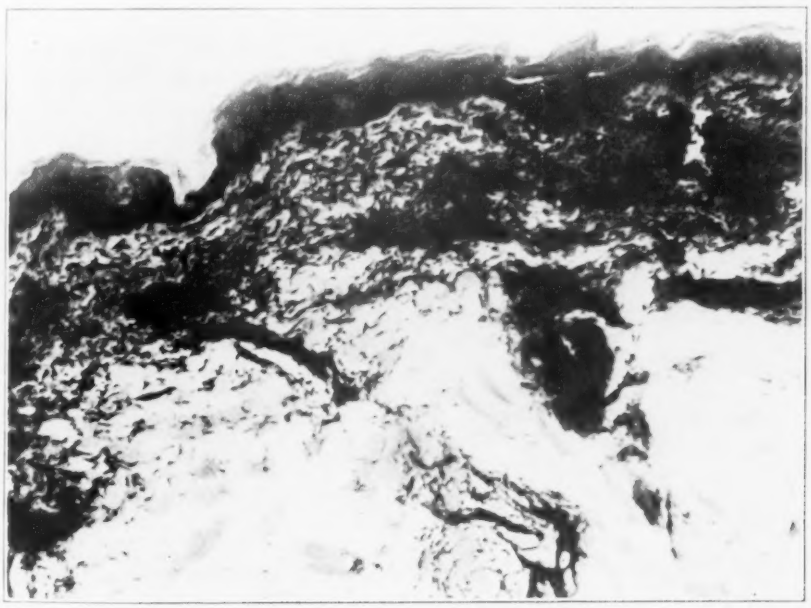

Fig. 2.—Material from the same biopsy specimen as in figure 1 but outside the treated area. Note the pronounced infiltration of the upper portions of the cutis and the masses of Hansen bacilli. × 150; green filter.

in the neighborhood showed corresponding pictures (figs. 1 and 2).

A specimen for biopsy was taken from the back in such a way as to include the area selected

The epidermis as a whole showed hypotrophy, containing only a few small rete processes. In some places the hypotrophy was particularly marked, and there were scattered patches of hyperkeratosis without parakeratosis.

The changes in the cutis were encountered particularly in one part of the section, while toward the other they gradually disappeared. There was an infiltration of cells in the upper layers of the cutis of the parts in which the changes were more pronounced, reaching the epidermal region. In the other part of the section there were a few isolated small cell infiltrations surrounding the blood vessels. Here Hansen bacilli were scarce and not easily detected, while in the aforementioned areas large quantities were present.

I was also keenly interested in the possible damage that might be caused to the skin by the action of the rays. However, fractional doses, even up to a total of 6,000 r, produced but a few patches of pigmentation or depigmentation after one and one-half to two and three-fourths years and 1 instance caused slight atrophy. This atrophy was, however, in no way different from that occurring on spontaneous healing of leprous lesions. Five thousand roentgens given in one sitting caused severe atrophy with telangiectases after the lapse of two and three-fourths years; hence I do not advocate the employment of a single application of that size.

Bacteriologic studies (from every lesion material was taken at least three or four times by scratching) revealed that in respect to the presence of organisms the effect of the treatment was nil, and bacilli were invariably found. The number of bacilli was somewhat reduced, which is also seen in the histologic pictures (Ziehl-Neelsen stain), where in the treated areas only a few bacilli were seen but in the surrounding tissue large masses of them were present.

In the same 2 patients scars which had developed after treatment with carbon dioxide also contained Hansen bacilli. Fresh infiltrations did not, however, stop at the border of the carbon dioxide–treated lesions.

In one of the lesions which showed depigmentation and anesthesia after irradiation pigmentation developed during the course of the treatment; it appeared, however, more slowly than in the surrounding tissue, while, on the other hand, its complete disappearance took less time than elsewhere.

Clinically normal skin was exposed to doses of 800 to 1,500 r. Here the bacilli remained uninfluenced, and newly developing eruptions did not stop at the border of the treated area.

From these experiments it may therefore be concluded that it is possible to influence local leprous infiltrations by means of grenz rays. But it seems to be of even greater importance that after exposure to sufficiently high amounts of rays recurrences do not tend to develop in the treated areas. A certain degree of local resistance seems thus to be created by irradiation. This fact might be made use of in the treatment of particularly disturbing lesions.

On the basis of these results, experiments are now being conducted in an attempt to influence leprous infiltrations of the face (facies leontina) and eyes.

SUMMARY

In 2 cases of leprosy of the mixed type the reactions taking place in leprous infiltrations as a response to exposure to grenz rays were recorded. On a total of eighteen cutaneous areas selected for irradiation doses of 600 to 8,000 r were applied in a single exposure or in several fractional exposures. The maximum voltage varied between 6 and 14 kilovolts, equivalent to half value layers of 0.021 and 0.033 mm. of aluminum. It was seen that on exposure to doses exceeding 2,000 r leprous infiltrations disappeared, although, as a rule, higher doses were required to produce that effect. It was a particularly striking feature that newly developing infiltrations in the surrounding skin halted at the border of the treated areas. Bacilli were constantly found in the lesions.

SPECTROGRAPHIC ANALYSIS OF GOLD IN THE SKIN FOLLOWING TREATMENT OF LUPUS ERYTHEMATOSUS

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During the past eight years, we have been studying a group of patients whose response to gold therapy had not been satisfactory from a clinical standpoint. These patients had received various amounts of gold sodium thiosulfate both by the intravenous and by the intramuscular route. In 1931 Monash and Traub [1] introduced a method of treatment for lupus erythematosus by means of intracutaneous injection of gold sodium thiosulfate and reported favorable response. The question then arose whether or not the presence of gold in lesions of lupus erythematosus under treatment with gold sodium thiosulfate had any effect in the healing of these lesions. In order to determine this point, it became desirable in this experiment to collect data with respect to the presence or absence of gold in normal skin, in active lesions and in healed lesions, as well as to study the relationship of the time element to the presence or absence of gold in the skin. Similar data were also desirable for the duration of detectable gold in the blood and urine following intravenous as well as intramuscular injections of gold sodium thiosulfate. In order to extend this study, a determination was made of the presence of gold in the skin and the various tissues of guinea pigs which had been given injections of gold sodium thiosulfate.

Spectrographic methods have been previously used successfully for the detection of gold in tissues and biopsy specimens of skin.[2] Gaul and Staud [2c] demonstrated the feasibility of spectroscopic analysis of cutaneous biopsy specimens as a means of demonstrating the presence of gold. They observed that gold was uniformly distributed in the skin of patients receiving gold sodium thiosulfate and stated that these deposits were of permanent nature. Chemical methods have also been used [3] for detection of comparatively large amounts of gold. In this study, spectrographic methods were necessary, as the quantity of gold present in a single biopsy specimen is considerably lower than can be satisfactorily demonstrated by chemical means. While the high frequency spark method of excitation has certain advantages,[2a] the direct current arc was used in our study because of the greater sensitivity.[4]

SPECTROGRAHIC METHOD

Spectrograms were made on a large Bausch and Lomb Littrow type instrument of 180 cm. focal length equipped with quartz optics. Carbon anodes were 5/16 inch (0.8 cm.) in diameter, 1 inch (2.5 cm.) long, drilled to a depth of 1/4 inch (0.64 cm.) with a 5/32 inch (0.4 cm.) drill; the cathode was ground to a point. With a gap of 4 mm. and a slit 20 microns wide, the arc was focused on the collimating lens, with the image of the anode screened off and the image of the tip of the cathode allowed to fall on the lens. Using bits of dried skin from a guinea pig that had been given injections of gold sodium thiosulfate loaded into the crater of the anode and current of 10 to 18 amperes at 220 volts (direct current), we found by the moving

From the Department of Dermatology and the Department of Industrial Hygiene, University of Pittsburgh School of Medicine.

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1. Monash, S., and Traub, E. F.: Modification Therapy with Gold Compounds in Lupus Erythematosus: Preliminary Communication, Arch. Dermat. & Syph. **24**:110 (July) 1931.

2. (*a*) Gerlach, W., and Gerlach, W.: Clinical and Pathological Applications of Spectrum Analysis, London, Adam Hilger, Ltd., 1934. (*b*) Burkhardt, L., and Gerlach, W.: Histologische und spektralanalytische Untersuchung der exhumierten Organe eines Goldarbeiters bei Verdacht auf Edelmetallvergiftung, Monatschr. f. Unfallh. **43**:136 (March) 1936. (*c*) Gaul, L. E., and Staud, A. H.: Clinical Spectroscopy: A Study of Biopsy Material Taken from Patients Receiving Gold Sodium Thiosulphate, Arch. Dermat. & Syph. **28**:790 (Dec.) 1933; (*d*) Clinical Spectroscopy: Quantitative Distribution of Gold in the Body or Its Physiopathologic Retention as a Reciprocal of the Capillary System, ibid. **32**:768 (Nov.) 1935.

3. Block, W. D., and Buchanan, O. H.: The Microdetermination of Gold in Biological Tissues, J. Lab. & Clin. Med. **28**:118 (Oct.) 1942; The Microdetermination of Gold in Biological Fluids, J. Biol. Chem. **136**: 379 (Nov.) 1940.

4. Armstrong, D. W., and Brackett, F. S.: Spectroscopic Analysis of Biological Fluids for Heavy Materials, J. Indust. Hyg. & Toxicol. **21**:448 (Nov.) 1939.

plate method that the first visible line at 2,427.98 and 2,675.95 angstroms appeared six to eight seconds after the arc was struck; consequently in the subsequent spectrograms of biopsy specimens the shutter was not opened till six seconds after the arc was struck. This had some effect in lighting the background on the plate.

Eastman no. 33 antihalation plates were used.

SENSITIVITY

By loading 0.2 cc. of appropriate dilutions of gold chloride into the crater of the anode, the sensitivity of the method was found to lie between 0.05 and 0.0025 micrograms of gold in the arc. The former amount gave easily perceived lines at 2,427.98 and 2,675.95 angstroms and the latter no detectable lines.

EXPERIMENTAL STUDY

Three male guinea pigs weighing approximately 2.2 Kg. were given injections of gold sodium thiosulfate. One animal received a total of 50 mg. (0.05 Gm.) in 0.4 cc. of sterile water intragluteally and was autopsied after two weeks. The second guinea pig received 1 mg.

TABLE 1.—*Spectrographic Analysis of Tissue of Guinea Pigs*

	Guinea Pig 1, 50 Mg. Au, Intramuscular	Guinea Pig 2, 1 Mg. Au, Intravenous	Guinea Pig 3, 1 Mg. Au, Intramuscular
Right thigh (site of injection)	Not done	Not done	+++++
Kidney	+++++	++++	++++
Liver	++++	+++	+++
Striated muscle	+++ (back)	+ (pectoral)	+ (pectoral)
Spleen	Not done	+++	Not done
Skin	++	+	+
Heart	Not done	+	+
Bone marrow	Not done	+	+
Brain	+	0	0

(0.001 Gm.) of gold sodium thiosulfate in 0.1 cc. of sterile water intravenously and was autopsied in ten days. The third animal received 1 mg. (0.001 Gm.) of gold sodium thiosulfate intramuscularly and was autopsied in fourteen days. Small portions of tissue, as nearly as possible the exact size of the biopsy specimens of human skin, were cut from the various organs of each animal. These were allowed to dry thoroughly under gauze; then they were loaded into the craters of the carbon anodes, and spectrograms were made with a current of 14 amperes, the shutter being opened six seconds after the arc was struck and the exposure continued for sixty seconds. The results of the spectrographic analysis of the various guinea pig tissues are given in table 1.

CLINICAL STUDY

Studies of Skin.—Cutaneous biopsies were made on a group of 26 patients under treatment for lupus erythematosus, selected over a period of eight years for this study. Twenty-four of these patients had failed to respond satisfactorily to gold therapy from a clinical standpoint, and the remaining 2 patients were chosen to complete this study from the standpoint of time interval. Specimens for biopsy were removed by the skin punch method outlined by Gaul and Staud,[2c] which consists of the taking of dermal biopsy specimens with a $\frac{3}{16}$ inch (0.47 cm.) punch, removing specimens weighing approximately 0.025 Gm. Specimens were taken from normal skin, from healed scars and from active lesions of lupus erythematosus. Each specimen was allowed to dry thoroughly in air and then was loaded into the crater of the anode. With the current adjusted to 14 amperes, the shutter was opened six seconds after the arc was struck and the plate exposed for sixty seconds. Plates were developed in D11 developer and fixed and hardened in potassium chromium alum. The accumulated plates were all examined at one time and the quantity of gold present assigned a rating based on the intensity of the line 2,427.98 angstroms. One plus designates the least perceptible yet definite line which could be seen under magnification, increasing density, of course, being designated by an increased number of plus signs, up to 5, which was the intensity comparable as nearly as possible to that of 1 microgram of gold in the arc. For the purposes of the study it was not felt necessary to employ a more precise quantitative method. The spectrographic-analytic data obtained on the cutaneous biopsies of the clinical patients are represented in table 2.

TABLE 2.—*Spectrogram of Skin*

Subject	Sex	Age, Yr.	Interval from Last Injection	Site of Biopsy *	Dose, Gm.	Spectrogram
1	F	34	7 days	N; R. arm	0.050	0
2	F	32	14 days	L; L. cheek (a)	0.050	0
3	F	43	60 days	N; L. leg	40.50	++++
4	M	42	60 days	N; L. arm	0.70	0
5	F	16	90 days	N; L. thigh	0.09	+
6	F	39	5 months	L; L. cheek (s) N; L. arm	5.25	+++ +++
7†	F	26	5 months	L; scalp (s) N; L. arm	7.20	+++ ++
8	F	26	6 months	N; L. arm	2.00	++
9	F	38	1 year	L; scalp (s)	10.05	++
10	F	26	2 years	N; L. arm L; L. chest (a)	30.95	0 0
11	F	23	2 years	N. L. arm L; S. scalp (s)	16.25	++ ++++
12	M	41	2 years	L; L. cheek (s) N; L. arm	58.45	+ ++++
13	M	39	2 years	L; L. cheek (s)	1.00	+
14	F	43	2 years	N; L. arm	10.25	0
15	M	44	2 years	N; L. arm	2.00	0
16†	M	51	2 years	L; L. cheek (a)	11.25	0
17	F	31	2 years	N; L. arm	12.50	+
18	F	46	3 years	N; L. leg	42.50	0
19‡	M	43	3 years	L; R. cheek (a)	2.50	0
20	M	39	4 years	N; R. leg L; R. cheek (s)	50.00	++++ ++++
21§	M	46	5 years	L; L. cheek (s)	1.50	+
22‡	F	41	7 years	L; nose (a) N; L. arm	5.00	0 ++
23	F	35	7 years	L; L. cheek (s) N; L. arm	10.25	+ ++
24	F	24	8 years	N; L. arm	5.25	+
25§	M	47	8 years	L; R. leg (s)	7.40	++++
26	F	48	15 years	L; L. cheek (a) N; L. arm	6.00	0 0

* Explanation of symbols: N, normal skin; L, lesion; (s), scar; (a), active lesion.
† Gold dermatitis.
‡ Carcinoma developed.
§ Gold pigmentation.

Studies of Blood.—Blood was removed from the cubital veins of 11 patients in amounts of 5 to 10 cc. at intervals varying from ten minutes to four weeks after an intravenous or intramuscular injection of gold sodium thiosulfate. The specimens were oxalated to prevent clotting. Two-tenths cubic centimeter of blood was pipetted into the crater of an anode and dried on

the oven for one hour at 110 C. The spectrogram was taken by the method used for biopsy specimens.

Studies of Urine.—Specimens of urine were collected from 8 patients receiving intravenous and intramuscular injections of gold sodium thiosulfate. All specimens analyzed, except the specimen obtained one hour after injection, were those voided in the morning on awakening. Two-tenths cubic centimeter of urine was pipetted into the crater of an anode and dried in the oven for thirty-five minutes at 105 C. The spectrograms were taken by the method used for biopsy specimens. The spectrographic data obtained on blood from patients receiving gold therapy are given in table 3, and those obtained on urine are given in table 4. For added information patch tests were performed on all patients with an ointment containing 1 per cent solution of gold sodium thiosulfate, all of which tests gave negative readings.

COMMENT

The distribution of gold in the tissues of the guinea pigs studied corresponded to the findings reported by other authors using the spectrographic [2 b, c] and microchemical [5] methods. The detectable gold was most pronounced in the kidneys and liver and at the sites of intramuscular injection, but gold was also detectable in the muscle, skin, heart, brain and spleen. A total of 26 patients, 9 males and 17 females, of ages ranging between 16 and 51 years were studied. A total of 36 biopsy specimens were removed

Fig. 1.—*20-S*, from scar of healed lesion on right cheek. Last injection of gold salt four years previously. *20-N*, from normal skin of right leg of same patient. *11-S*, from scar of healed lesion on scalp. Last injection of gold salt two years previously. *11-N*, from normal skin of left arm of same patient. Gold was detectable in all spectrograms.

Fig. 2.—*23-S*, from scar of healed lesion. Last injection of gold salt seven years previously. *23-N*, from normal skin of left arm of same patient. *6-S*, from scar of healed lesion. Generalized gold pigmentation present. Last injection of gold salt five months previously. *22-N*, from normal skin of arm. Last injection of gold salt eight years previously. Gold was detectable in all spectrograms.

TABLE 3.—*Spectrogram of Blood*

Subject	Dose, Gm.	Route	Time of Collection of Specimen	Spectrogram
1	0.050	Intravenous	10 minutes	++++
2	0.050	Intravenous	20 minutes	++++
3	0.050	Intravenous	30 minutes	++++
4	0.050	Intravenous	1 week	++++
5	0.025	Intramuscular	1 week	+
6	0.010	Intramuscular	1 week	+
7	0.0025	Intramuscular	2 weeks	+
8	0.025	Intramuscular	2 weeks	+
9	0.025	Intramuscular	2 weeks	+
10	0.025	Intramuscular	3 weeks	+
11	0.025	Intramuscular	4 weeks	0

TABLE 4.—*Spectrogram of Urine*

Subject	Dose, Gm.	Route	Time of Collection of Specimen	Spectrogram
1	0.025	Intravenous	1 hour	+++
2	0.025	Intramuscular	24 hours	++
3	0.025	Intravenous	24 hours	++
4	0.025	Intravenous	72 hours	++
5	0.025	Intravenous	72 hours	++
6	0.025	Intramuscular	72 hours	+
7	0.025	Intravenous	1 week	+
8	0.025	Intravenous	1 week	0

5. Block, W. D.; Buchanan, O. H., and Freyberg, R. H.: A Comparative Study of Distribution and Excretion Following Intramuscular Injection of Five Different Gold Compounds, J. Pharmacol. & Exper. Therap. **73**:200 (Oct.) 1941.

for spectrographic detection of gold. Sixteen specimens were removed from active lesions and healed scars of lupus erythematosus, and 20 specimens were removed from normal skin of various parts of the body. From only 9 patients were we able to obtain biopsy specimens from both the lesion and the normal skin. The biopsy specimens were obtained as early as one week following an injection of gold sodium thiosulfate and as late as fifteen years after the last known injection. One patient of this group manifested gold pigmentation, and in 1 patient gold dermatitis developed during the course of treatment. In 3 patients, epithelioma developed within the lesion of lupus erythematosus. In analysis of 20 biopsy specimens of normal skin gold was detectable spectrographically in 13 instances in patients who had received a total dose of gold sodium thiosulfate ranging from 5.06 to 58.45 Gm. with a time interval of sixty days to seven years following the last known injection. In 7 instances, gold was not detectable spectrographically in the normal skin of patients whose total dose varied from 2 to 42.50 Gm. after a time interval of seven days to fifteen years after the last known injection of gold. The absence of detectable gold after periods of two, three and fifteen years, except in 2 instances, in which gold was not detectable in the normal skin after seven and sixty days in amounts of 0.05 Gm., differs from the observations previously reported [2c] that gold is permanently deposited in the skin.

The analysis of the spectrograms of skin removed from active lesions and scars of healed lupus erythematosus revealed some interesting and rather striking facts. Of a total of 16 spectrograms, 6 from active lesions and 10 from scars of healed lesions, it was found that gold was not detectable spectrographically in the active lesions of lupus erythematosus. These patients had received a total dose of 0.05 to 30.95 Gm. of gold sodium thiosulfate, and the biopsy specimens were removed fourteen days to fifteen years after the last known injection. Jones and Alden,[6] in a report on the use of gold by subcutaneous injection in treatment of lupus erythematosus, cited Wigley, who reported the absence of demonstrable gold in the diseased skin following the intravenous use of gold chloride but stated that the skin of patients who had exfoliative dermatitis from the use of this drug contained fairly high concentrations of gold. However, gold was detectable spectrographically in every biopsy specimen, 10 in all, removed from a healed scar of lupus erythematosus of patients who had had a total dose of 1.50 to 58.45 Gm. of gold sodium thiosulfate, taken at intervals of five months to eight years after the last known injection.

From the analysis of the small group of patients studied we cannot draw absolute conclusions, but it is our impression that the presence of gold in the lesion of lupus erythematosus under treatment with gold sodium thiosulfate is associated with healing. In every instance in our series of patients gold was detectable spectrographically in the healed scars of lupus erythematosus, but uniformly gold was not detectable in any active lesion of lupus erythematosus in this study. The absence of gold in the active lesion of lupus erythematosus under treatment with gold therapy may account for the unfavorable clinical response which we encountered in the use of the intravenous and intramuscular method of injection; whereas, the favorable response reported by Monash and Traub [1] may have been due to the direct deposition of gold into the lesion by intracutaneous injection.

Gold was detectable in the blood from ten minutes until three weeks after a given injection. No gold was detectable one month after injection, whether given intravenously or intramuscularly. Block, Buchanan and Freyberg,[5] using a microchemical method, reported that gold was present in the plasma and absent in the red blood cells of patients receiving gold therapy. We did not attempt to include this differentiation in our study.

Gold was detectable in the urine one hour up to one week after injection but was more easily detectable during the first seventy-two hours after injection.

The presence of gold was detectable spectrographically in healed scars and normal skin but was not detectable spectrographically in active lesions.

5026 Jenkins Arcade.
7026 Jenkins Arcade.

ABSTRACT OF DISCUSSION

DR. EUGENE F. TRAUB, New York: This presentation is the first attempt that I know of to explain the local effect of gold compounds. It is particularly interesting, of course, to me because I do not believe many men utilized the method that Dr. Monash and I suggested, because they probably thought, as we do now, that it was just another method of treatment that was effective sometimes and ineffective and painful at other times.

Dr. Jacob and Dr. Beinhauer asked me to discuss their paper and give some of the details of our method of local treatment. I will gladly do so because I think some of the criticism that was leveled at the method was because of a misunderstanding of how it was to be employed.

I know, for instance, that at one of the institutions in New York where it was tried, sloughs and other

6. Jones, J. W., and Alden, H. S.: Modification of Therapy with Gold Compounds in Lupus Erythematosus, Arch. Dermat. & Syph. **28**:544 (Oct.) 1933.

unpleasant results were reported, because it was attempted to give 1 cc. intradermally at a site. I do not believe that so much can be given. In other words, we used 1 minim (0.0616 cc.) at a site and not 1 cc. We used 1 per cent solution of gold sodium thiosulfate and incorporated it in procaine hydrochloride, and we preferred not to have epinephrine in the procaine hydrochloride. While the injections are slightly painful, I have not had any one discontinue treatment for that reason.

We selected for such treatment localized discoid patches in patients who had failed to respond to intravenous or other types of treatment, never patients with generalized lupus erythematosus. Each patient's case was thoroughly studied from a general medical standpoint, and the local treatment was simply the most effective way of getting gold into the subject in our opinion.

At the time that we first attempted to find out whether gold would be of any help in this way, we studied also other heavy metals, such as nickel and copper, and also tried injections of a sterile milk preparation and other agents to determine whether or not it was just a local inflammatory reaction that produced results or whether it might actually be the effect of the gold itself in the local site. We were not able to prove one way or another whether that was true. We found that gold seemed to be more effective than the other agents that we tried.

One of the other things that we felt in the beginning was that each lesion had to be treated individually; that if it was not treated individually, it did not respond. That, I know now, is not true, because we have now treated approximately 100 patients locally, and in the majority that have responded to such treatment, lesions that were not individually treated sometimes responded and disappeared.

We have had no complications at all from the method of treatment. In fact, our idea in the beginning was that it would avoid any complications and reactions. In fact, it was the great many unpleasant reactions to gold that were occurring that made us look for another method of administration rather than the intravenous. Neither have we had any unpleasant results locally, nor have we had any general reactions. Not all our patients have responded to this treatment. It is only fair to say only a fraction of the patients so treated will respond. On the other hand, we have had some excellent results with relatively few injections in patients that have had as many as a hundred or more intravenous injections wthout result.

Directly after we published this preliminary report, Gougerot used the method extensively and reported his results in several articles in the French literature. He claimed excellent results in the treatment not only of lupus erythematosus but of lupus vulgaris and other types of localized cutaneous tuberculosis, and, if our report was conservative, he was perhaps overenthusiastic in praising the method and describing his many excellent results.

The important point that Drs. Jacob and Beinhauer brought out, of course, is the fact that gold was found in the scars of healed lesions and in the normal skin of a great many patients treated with gold. But they failed to find gold in active lesions of lupus erythematosus that had not responded well. This would seem to indicate that the gold must be in the lesion itself in order for the treatment to be effective.

The intradermal method is one that can be safely employed by any one who is qualified to give a proper intradermal injection of any kind. It is only necessary to inject 1 minim (0.0616 cc.) at each of several sites about the periphery of every patch. I hope to get into contact with some of our patients on whom we used the method locally and get specimens to submit to Dr. Jacob and Dr. Beinhauer to see whether or not that may throw some additional light on this subject.

Not having had any experience with the spectroscopic analysis of sections of skin, I was glad to hear the paper.

Samuel M. Peck, M.D., Bethesda, Md.: It is a privilege to listen to a paper which attempts to cast additional light on the chemotherapeutic action of some of the drugs which one uses routinely in the treatment of disease.

The criticism leveled against the local use of gold by Monash and Traub was that they were attempting to treat a generalized disease by local therapy alone. This was especially pertinent, because it was thought that gold therapy for lupus erythematosus exerted its beneficial effects systemically and not by a direct action on the lesion itself. Even the discoid type of lupus erythematosus is considered by many dermatologists to be a local manifestation of a generalized vascular disease.

With the presentation of the paper of Jacob and Beinhauer, some of the ideas on the mechanism of the action of gold in lupus erythematosus will have to be revised. One is tempted to deduce from their presentation that gold acts locally to produce its healing effects. The authors have as yet not been able to explain why no gold was found in the lesions which were still active. Perhaps local injection of gold salts into active lesions which fail to respond to the gold therapy might prove therapeutically helpful.

Dr. Fred M. Jacob, Pittsburgh: This work was prompted by several considerations: first, the poor response of certain of our patients; second by the question of gold pigmentation (we had 1 case of gold pigmentation around the scar following intravenous injection) and the question of deposit of gold in the skin, leading to the possible pigmentation of these skins later.

All have seen the pigmentations that occur at the elbow, sometimes at the site of puncture and sometimes when the gold escapes from the vein. So we wanted to convince ourselves, by means of some of our earlier patients, who had been exposed for years to sunlight, that the gold would not cause pigmentation after a period. The records of biopsies in these cases were all collected, and most of the ones on the first chart had been done before we began to evaluate our results. We put the results on the blackboard one day, and were rather astounded to see the curious findings of gold in the healed scar, gold in the normal skin and no gold in active lesions.

We also checked on the deposits of metals of other kinds, bismuth and mercury, particularly at the same time. In performing biopsies, we took specimens from syphilitic patients and from some of the patients with lupus who had been treated with bismuth as well. We studied the syphilitic skins for bismuth, mercury and arsenic, and the results were not at all striking. I think that there was 1 case in which bismuth showed after a considerable amount had been given. So there was very little deposit, at least in our cases, of bismuth or mercury or arsenicals in the skin, but the gold was not difficult to find.

As Dr. Beinhauer suggested, we began the studies microchemically, but the results were bad. Fortunately, we had the cooperation of the Department of Industrial Hygiene, and we were able to continue this work spectrographically.

APLASTIC ANEMIA WITH ACUTE AGRANULOCYTOSIS, THROMBOPENIC PURPURA AND COMPLICATING MAPHARSEN THERAPY

REPORT OF A CASE, WITH PATHOLOGIC OBSERVATIONS

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Many cases of aplastic anemia have been reported as resulting from the use of arsphenamine and several from the use of neoarsphenamine.

Rein and Wise [1] in 1939 reported a case remarkably similar as regards the aplastic anemia to the present one. This case is reviewed in table 2. The platelet count and the white blood cell count were somewhat higher than those of the present case, but otherwise the laboratory data were comparable. The diagnosis was aplastic anemia alone, without thrombopenic purpura and agranulocytosis in addition.

Kirkham and Perlmutter [2] in 1941 reported a second case, which had been observed in 1939. This is also reviewed and is compared with the present case in table 2. Their patient was reported to have had no platelets, but the red and white blood counts were, again, quite similar. An "athrombocytic" purpura was evidently present in addition to the aplastic anemia.

The following case report illustrates again the necessity of observation of the skin before each injection of an arsenical and notes the third reported instance of another possible danger from the usually nontoxic drug mapharsen.

TABLE 1.—*Laboratory Data and Progress, Present Case*

	Date, 1943									
	5/29	5/30 (a.m.)	5/30 (p.m.)	5/31	6/1	6/2	6/3	6/4	6/5	6/6*
White blood cells	2,100	1,800	1,400	700	1,010	1,000	1,000	850	900	600
Differential count										
Polymorphonuclears, per cent	2	4	..	1	..	..	2	2	8	..
Lymphocytes, per cent	98	96	100	99	..	..	98	94	90	96
Mononuclears, per cent	..	..	..	..	..	..	..	4	2	4
Red blood cells, millions	2.16	2.42	2.81	2.51	2.8	2.52	2.02	2.2	2.71	2.5
Hemoglobin										
Per cent	47	48	50	51	50	59	42	52	65	60
Grams	..	..	..	..	..	9	..	8	10.5	..
Reticulocytes	..	..	..	..	..	..	None	..	..	..
Platelets	77,000	..	..	..	..	..	..	..	46,070	..
Bleeding time, min.	3½	..	..	..	..	..	2	..	..	..
Clotting time, min.	15	..	..	..	..	..	4	..	..	..
Color index	1.1	..	..	..	..	..	1.5	..	..	..
Urine	..	..	..	Normal	..	..	..	..	..	..
Kahn reaction	..	..	..	—	..	..	..	..	..	..
Icteric index	8	..	..	..	..	10	..	..	..	..
Blood sugar, mg./100 cc.	..	..	..	..	..	134	..	..	..	..
Blood urea, mg./100 cc.	..	..	..	..	..	15	..	..	..	..
Albumin-globulin ratio	..	..	..	..	..	1:1.34	..	..	..	..
Dextrose tolerance	Normal	..	..	..	..	..	..	..	..	..
Sternal marrow	..	..	..	..	..	..	..	96% normal lymphocytes; 4% lymphoblasts; no young erythrocytes seen; smear contained a large amount of fat		
Transfusions, cc.	..	500	300	300	300	..	500	..	500	

* Date of death.

REPORT OF CASE

A man aged 37, of Syrian ancestry, gave a history of having had syphilis for twenty years and of having taken treatments irregularly over a period of two years until January 1943. When treatment was first begun, he had several febrile reactions, but with this exception, thereafter he had tolerated his previous treatments with no history of apparent reactions. At that time neoarsphenamine was the arsenical employed, but the exact amount and dosage are, unfortunately, unknown.

In March 1943 the patient entered military service. At one station he was found to have a positive serologic reaction and further therapy was advised. Mapharsen was the arsenical used. On May 18, 1943 the patient

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1. Rein, C. R., and Wise, F.: Mapharsen in Treatment of Syphilis in Office Practice, J. A. M. A. **113**: 1946-1952 (Nov. 25) 1939.

2. Kirkham, D., and Perlmutter, M.: Fatal Aplastic Anemia Following the Use of Mapharsen: Report of a Case, Arch. Dermat. & Syph. **43**:111-115 (Jan.) 1941.

first noticed the beginning of a purpuric eruption on the arms and forearms. He was at that time receiving mapharsen (0.06 Gm. twice weekly) and bismuth subsalicylate weekly. After he received the tenth injection of the first course of mapharsen, the purpura appeared. The physician who was treating him was informed, but,

TABLE 2.—*Comparison of the 3 Cases*

Authors	1. Rein and Wise	2. Kirkham and Perlmutter	3. Freeman
Age	30	24	37
Sex	F	F	M
Ancestry	Unstated	Italian	Syrian
Previous history of reactions to drugs	Nausea and vomiting from mapharsen	Nausea and "weakness" (nitritoid ?, [H. E. F.]) from mapharsen	Febrile reactions to neoarsphenamine; sensitivity to salicylates
No. of mapharsen injections previously given	15	19	12
Chief complaint	Pallor, weakness and fainting	Vaginal bleeding	Skin eruption and fainting attack
Purpura and ecchymoses	Lower extremities	Extremities and trunk	Widespread
Lymphadenopathy	Yes	No	Yes
Temperature	Up to 105.2 F.	Up to 105 F.	Up to 105.6 F.
Necrotic ulceration of throat	Not noted	Yes	Severe
Number of days surviving	30	7	19
White blood cells	4,100 to 2,200	2,425 to 750	2,100 to 600
Red blood cells	3.1 to 1.5 millions	2.62 to 1.06 millions	2.81 to 2.02 millions
Hemoglobin	62 to 42%	51 to 16%	65 to 42%
Lymphocytes as high as	90%	100%	100%
Platelets as low as	100,000	0	46,070
Reticulocytes	0.5%	0	0
Bleeding time	4 minutes	20 minutes +	2 to 3½ minutes
Clotting time	5 minutes	5 to 6 minutes	4 to 15 minutes
Color index	1.4, 0.9	..	1.1, 1.5
Icteric index	5.5	6	8, 10
Blood urea nitrogen	"Normal blood chemistry"	29	15
Organism cultured from blood (day of death)	..	Hemolytic streptococci	Hemolytic streptococci

nevertheless, two more injections of mapharsen were given in spite of the purpura. The total amount of recent treatment was, then, five injections of the bismuth preparation and twelve of mapharsen.

I first observed him, at another station, on May 28, 1943. This was ten days after the onset of the purpura and about four days after the last dose of mapharsen had been administered. At that time a generalized petechial and ecchymotic eruption on the skin and oral mucous membranes was observed. The patient did not consult the dermatologist because of his rather severe purpura but because of a coincidental impetigo contagiosa of the face. He was much more concerned about the impetigo than about the purpura because the previous physician had ignored the purpura entirely even after his attention had been called to it.

A history of extreme sensitivity to salicylates was obtained, as was a recent history of moderate constipation, anorrhexia and asthenia.

He was well developed, and his general physical condition was normal except for the cutaneous lesions and a moderately severe generalized lymphadenopathy. The blood pressure was 118 systolic and 80 diastolic.

In view of the history and clinical observations the following diseases were considered after preliminary examination: (1) blood dyscrasia due to mapharsen (arsenical thrombopenia?), (2) infectious mononucleosis, (3) monocytic leukemia and (4) purpura of other origin than that of drug intoxication.

Hematologic and other diagnostic studies were begun. During the night the patient, incidentally, became faint, presumably from his severe anemia. The temperature was 101 F. on admission and 104 F. the next day, although there was no congestion of the lungs.

The first blood smears indicated that the severe anemia was aplastic, with agranulocytosis, and it was recognized that the prognosis was grave. These observations and other laboratory data are shown in table 1. Staining of blood smears with Goodpasture's stain showed no peroxidase-positive cells.

On the second day one of the larger of the many purpuric lesions on the distal medial surface of the left thigh was indurated and was beginning to become pustular. This later became necrotic and ulcerated.

The temperature remained between 102 and 105.6 F., but salicylates could not be given. Hydrotherapy was used in an attempt to reduce the fever. Six transfusions of citrated blood (300 to 500 cc.) were given and pentnucleotide, crude liver extract and vitamin K were administered for whatever effect they might have.

After five days the patient had gradually become more prostrated and was apprehensive. His liver and spleen became moderately enlarged and tender. Some of the larger ecchymotic areas of the oral mucous membrane became ulcerated, and swallowing became difficult. A sternal puncture was made at this stage.

TABLE 3.—*Pathologic Observations in 3 Cases*

Rein and Wise	Kirkham and Perlmutter	Freeman
Aplastic anemia due to arsenic treatment for syphilis	Aplasia of bone marrow	Aplastic anemia
Multiple petechial and ecchymotic hemorrhages of the arachnoid, visceral pleura, epicardium, myocardium, endocardium, renal capsules, ileum and cecum	Necrotizing pharyngitis	Hemorrhages, generalized and severe, of skin, mucous membranes and serous surfaces
	Splenomegaly	Severe subacute ulceronecrotic stomatitis, pharyngitis, laryngitis, tracheitis and bronchitis
	Multiple hemorrhages in the viscera	Severe bilateral confluent lobular pneumonia
Toxic hepatosis	Microscopically	Tuberculous primary complex
Bilateral ovarian hemorrhagic cysts	Much fatty tissue and few hemopoletic cells in sternal marrow	Generalized arteriosclerosis, slight
Hyperplastic splenitis	(A few gram-positive bacilli seen in a section of the bone marrow)	Bilateral moderate inguinal and axillary lymphadenopathy
Sanguineous peritoneal fluid		Ulcer of the skin, medial aspect of the left knee
		Hepatomegaly, moderate
		Acute toxic splenitis, moderate
		Fatty metamorphosis of liver, mild

The patient's condition became progressively worse. Bilateral corneal and conjunctival hemorrhages developed; gingival bleeding was rather severe, and he was dyspneic and semicomatose. A left submaxillary cellulitis was indurated and edematous. The cutaneous ecchymoses became more notable and almost confluent. The patient died on his ninth day in the hospital, nineteen days after he first noticed his purpura.

Pathologic Examination.—At autopsy, severe ulceronecrotic lesions were found throughout the mouth and upper respiratory tract. Hemorrhages were present in the skin, mucous membranes and serous membranes, and there was a bilateral confluent lobular pneumonia. The marrow of the ribs and vertebrae was reddish gray and was not remarkable grossly.

Microscopically, the ulceronecrotic lesions revealed widespread bacterial invasion but the tissue defense was restricted to scattered lymphocytes and plasma cells. There were no polymorphonuclear leukocytes. In the lungs there were numerous foamy pigmented phagocytes but, again, no polymorphonuclear cells. The bone marrow displayed aplasia of all elements, with only small, scattered, sparsely cellular foci. These foci were composed of lymphocytes, plasma cells, immature red cells and occasional "blasts."

In no organs were any leukemic infiltrations found, and there was no evidence of any leukemic change in the lymph nodes, spleen or liver. There was also no tendency for any particular type of cell to predominate in the scattered cellular areas in the bone marrow.

The pathologic observations in the 2 previously reported cases are compared with those of the present case in table 3.

COMMENT

The etiologic factor in this case is considered to have been the trivalent arsenical which was administered before the onset of the purpura. It is true that a blood dyscrasia such as this could be spontaneous or occur without known cause. However, the knowledge that arsenic can produce such a complication and its presence following arsenical treatment make logical the conclusion that the cause was arsenic. It is true that the patient had received bismuth subsalicylate, but he had none of the common symptoms of salicylate intoxication. No explanation is offered as to why the complication did not follow earlier treatment with neoarsphenamine.

No evidence of infectious mononucleosis or aleukemic leukemia was found.

CONCLUSIONS

In this case fatal aplastic anemia with thrombopenic purpura and agranulocytosis was a rare complication of mapharsen therapy.

704 Professional Building.

GRANULOMA ANNULARE AND MEASLES

CAPTAIN NORMAN M. O'FARRELL
MEDICAL CORPS, ARMY OF THE UNITED STATES

Although the treatment of the ordinary case of granuloma annulare, in which there are present only a few lesions on the backs of the hands, is not a difficult problem, one is often puzzled in the case of a child when the lesions are so numerous as to make treatment either with roentgen rays or with destructive methods impractical. The following experiences may be of help and may stimulate thought as to the cause of this little understood disease.

REPORT OF CASES

CASE 1.—A girl aged 7 years was seen with granuloma annulare of eighteen months' duration. There were present on the right ankle the original lesion, at the time of observation a palm-sized plaque, and more than forty smaller lesions, the majority on the legs but a few on the hands and abdomen. Biopsy was not made, but the diagnosis was corroborated by another dermatologist. The original lesion had been given 600 r of roentgen rays before I saw the child. The mother said that the lesion was flatter after the treatment but that new lesions had continued to appear.

Because it was felt that the further use of roentgen rays was impractical and the destruction of each area undesirable, the child was simply observed at monthly intervals. Several new rings appeared. When the child was brought in at the end of three months, all the lesions were gone. The mother reported that the girl had had measles, with a temperature of 105 F., and that when she got out of bed the involved areas were clear. Examination disclosed slight pigmentation at the site of the original lesion on the ankle but there was no remnant of any other lesion. To date, sixteen months later, there has been no recurrence.

CASE 2.—A girl aged 5 years, the daughter of an Army chaplain, was seen at the station hospital clinic and found to have typical lesions of granuloma annulare on the extensor surfaces of her hands, feet and legs, with occasional lesions on the thighs, more than two dozen in all. Mindful of the experience in case 1, a watchful attitude was maintained. Less than three weeks later the child contracted measles, had an elevation of temperature of unknown degree (but said by the mother to have been high) and when seen two weeks later was free from all lesions. No biopsy was made, as there was no question as to the diagnosis. There has been no recurrence of the granuloma annulare in an interval of three months.

CASE 3.—An Army lieutenant, 25 years of age, had granuloma annulare, with lesions limited to the backs of his hands and fingers. Shortly after he was seen for the first time he had acute nasopharyngitis with a temperature of 103.2 The lesions on his hands have not been influenced by this fever. He has never had measles.

SUMMARY AND CONCLUSIONS

Of 3 patients with granuloma annulare 2 recovered after having measles. The fact that the third patient did not recover after a febrile interlude suggests, although of course it does not prove, that the recovery of the 2 was due to a specific immunity reaction from measles. While it is true that there is occasionally spontaneous healing of granuloma annulare, the dramatic cure after measles in 2 cases was not likely to have been a coincidence.

From the Eighty-First General Hospital, Forney General Hospital, Palm Springs, Calif.

UNSUCCESSFUL TREATMENT OF AMERICAN LEISHMANIASIS WITH PENICILLIN

REPORT OF A CASE

MAJOR JAMES S. SNOW

MEDICAL CORPS, ARMY OF THE UNITED STATES

Leishmaniasis americana as observed in the Panama Canal Zone is a serious disease. It is not self limited but is progressive and destructive. Present treatment is prolonged, and recurrences are not uncommon. As the opportunity recently presented itself to treat a patient with this disease with penicillin, I wish to report my observations.

REPORT OF CASE

A 52 year old brown Panamanian man entered Gorgas Hospital on April 12, 1944, with a large ulcerated lesion of the face. He stated that this had started on the bridge of the nose about six weeks previously. He was employed in the Canal Zone as a carpenter and lived in a small rural community just outside the Zone.

The lesion involved the entire surface of the nose and extended laterally on each cheek. The ulcerated area was raw and granulomatous and measured 6.5 cm. from the bridge of the nose to the nares and 7.5 cm. transversely. Beyond this was a raised, firm border with surrounding cellulitis, producing considerable edema of the face. Pronounced regional lymphangitis extended downward across each cheek terminating in large palpable nodes at the angle of the mandible bilaterally. The remainder of his physical examination revealed nothing abnormal.

On examination the urine was normal. Hematologic examination showed 70 per cent hemoglobin, 4,000,000 red blood cells and 6,800 white blood cells, with 64 per cent polymorphonuclear leukocytes, 4 per cent eosinophils and 32 per cent lymphocytes. The Kahn and Wassermann reactions of the blood were both reported as "doubtful." The sedimentation rate of the blood was 53 mm. in the first hour. Roentgen examination of the chest showed normal conditions.

On April 13, tissue was removed from the active border for microscopic examination. This was examined by Dr. B. H. Kean,[1] who reported as follows: "The superficial and deep layers of the corium are occupied by an intense chronic inflammatory reaction in which lymphocytes and large macrophages predominate, although plasma cells are also present. There is no acute focal inflammatory reaction, but neutrophils are scattered throughout the tissue and a few eosinophils are also seen. Scattered throughout the tissue, both within macrophages and also within intervening spaces, are encapsulated round or oval parasites, averaging 4 microns in diameter. These contain small basophilic nuclei and the typical parabasal leishmania bodies.

Therapy with penicillin was started on April 23 and was given as follows:

April 23: 120,000 Oxford units of penicillin sodium was given intramuscularly, divided into six doses given at intervals of three hours. An additional 10,000 units diluted with 40 cc. of isotonic solution of sodium chloride was used topically as a wet dressing.

April 24: 117,000 units was given intramuscularly according to the same schedule, and 10,000 units was used topically.

April 25: 120,000 units was given intramuscularly and 10,000 units used topically.

April 26: 112,000 units was given intramuscularly and 10,000 units used topically.

April 27: 90,000 units was given intramuscularly and 10,000 units used topically.

During the five day period of treatment a total of 559,000 units of penicillin was given intramuscularly and 50,000 units was used in topical applications.

On May 5, eight days after the completion of the penicillin therapy, the lesion appeared somewhat improved in that the cellulitis had subsided and the lymphangitis and adenitis were less evident. The large ulcerated area was clean but showed no tendency to heal. A second specimen of tissue was then taken from the raised border immediately adjacent to the site of the original biopsy specimen.

The second biopsy specimen was examined by the same pathologist, who reported as follows: "The superficial and deep parts of the corium are occupied by a diffuse, extensive, chronic inflammatory reaction. Lymphocytes predominate in the reaction, but macrophages and plasma cells are also numerous. Collections of polymorphonuclear leukocytes are seen here and there, but there is no abscess formation. In the superficial parts of the corium a few leishmania bodies having typical nuclei and parabasal rods are seen. Part of the fresh tissue was crushed, smeared and stained according to the Giemsa technic. A few leishmania bodies are also seen in these preparations."

It was difficult to compare the number of parasites present in the two specimens, as in both instances they

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1. Pathologist, Board of Health Laboratory, Gorgas Hospital, Ancon, Panama Canal Zone.

d to be searched for carefully. However, the fact at well formed, apparently normal parasites were und in appreciable numbers in the second specimen dicates that leishmania organisms are probably not lnerable to penicillin. The clinical improvement in e cellulitis and lymphangitis was attributed to the neficial effect of the penicillin on the secondary pyo-enic infection present.

Treatment with antimony and potassium tartrate was rted May 9 and given every other day. After five eks of treatment (1.6 Gm. of the drug) the lesion s almost healed. This same response would have en expected had no previous therapy been used.

COMMENT

The results of treatment in a single case must f course be evaluated with caution and should not be considered conclusive. It is also possible that larger doses of penicillin may be effective in treatment of this disease. I wish merely to report my observations in this case, so that they may be added to the rapidly accumulating data about this remarkable new drug.

SUMMARY

A patient with leishmaniasis of the face did not respond to five days' therapy with penicillin. Well formed parasites were still found in the tissue eight days after completion of the treatment.

Gorgas Hospital.

DERMATITIS FROM PENICILLIN

REPORT OF TWO CASES

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Considering the large number of patients receiving penicillin and of physicians, nurses and others exposed to the drug while administering it, the incidence of true contact dermatitis from penicillin reported to September 1944 is not large. Pyle and Rattner [1] reported the first case. The reactions in 2 cases reported by Graves, Carpenter and Unangst [2] occurred in patients receiving injections of penicillin and were not contact dermatitis. They had received no previous medication with penicillin. The reaction was immediate and involved the hands, feet and groin.

The following 2 cases of dermatitis from penicillin occurred in the medical staff of hospitals.

REPORT OF CASES

CASE 1.—Dr. A. B., aged 27, began the administration of penicillin about March 1, 1944, in the surgical service at St. Luke's Hospital, Cleveland. In the latter weeks of the same month, dermatitis of the skin of the upper extremities and face appeared. There were cyclic recurrences until August 7. During this period he regularly administered solutions of sodium penicillin to patients in the hospital.

Examination on August 7 showed a dermatitis of the flexor surfaces of the wrists and forearms and of the cubital spaces, lower half of the arms and forehead. The primary lesion was a tiny vesicle on a diffuse erythematous base. There was fine desquamation. Pruritus was moderate. There was a focus of dermatophytosis pedis on the webs of the toes. The skin of the hands was normal. We attribute the absence of dermatitis here to the frequent washing necessitated by his hospital duties. The diagnosis was acute contact dermatitis.

The contactants suspected were penicillin, ammoniated mercury ointment U. S. P. and a white soap supplied at the hospital. Contact tests were made. There was no cutaneous reaction to the mercury preparation and the hospital soap. Sodium penicillin was diluted with isotonic solution of sodium chloride so that 1 cc. contained 5,000 units. There was a strong positive reaction to the solution of sodium penicillin in forty-eight hours. A few days later, a strong positive reaction was obtained within six hours to an intradermal injection of solution of sodium penicillin of the same strength and to a second patch test. Since then, Dr. A. B. has avoided or minimized exposure to the solution of penicillin, with no recurrence of the cutaneous irritation.

The reaction in case 2 was of a different character.

CASE 2.—Dr. R. L., aged 26, began the administration of solution of penicillin in November 1943 in the medical service of University Hospitals, Cleveland. There was no history of previous cutaneous maladies except a focus of interdigital dermatophytosis pedis. The dermatitis appeared six weeks after the first exposure to penicillin. There was erythema of the cheeks in a butterfly area. Erythema and dermatitis involved the upper lids of both eyes, base of the nose, lateral border of each hand and sides of the little fingers. Penicillin was suspected as the cause of the dermatitis and was avoided for two weeks. During this time, the dermatitis slowly cleared. There has been no recurrence of symptoms. The impression was that the reaction was either a seborrheic dermatitis or a contact dermatitis due to penicillin.

Contact tests were made with solution of penicillin, ethyl alcohol, 1:1,000 solution of mercury bichloride and liniment of soft soap U. S. P. on the flexor surface of the right forearm. All reactions were negative in forty-eight hours. An intradermal injection of 0.1 cc. of solution of penicillin (500 units) gave no reaction during ninety-six hours of observation.

Later he gave himself 60,000 units of penicillin intramuscularly in one dose. Within six hours there was pruritus of the hands and feet. In twenty-four hours there was a papular eruption of the hands and feet. This was followed by subsidence of the edema and desquamation.

Later 3 drops of solution of penicillin (5,000 units per cubic centimeter) was instilled into the conjunctival sac of the left eye. A patch test was applied to the face below the right eye. There was no reaction to either of these tests.

COMMENT

The dermatitis in the first case was of a greater degree and involved a larger cutaneous area than that in the second case. The penicillin patch tests gave immediate reactions.

In the second case there was much less dermatitis both in severity and in extent. No epidermal or intradermal sensitivity could be shown by cutaneous tests. Because of the failure to react to the cutaneous tests and the failure

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1. Pyle, H. D., and Rattner, H.: Contact Dermatitis from Penicillin, J. A. M. A. **125**:903 (July 29) 1944.

2. Graves, W. N.; Carpenter, C. C., and Unangst, R. W.: Recurrent Vesicular Eruptions Appearing During Administration of Penicillin, Arch. Dermat. & Syph. **50**:6 (July) 1944.

react to subsequent exposure to penicillin solution, the final diagnosis in this case was gonorrheic dermatitis. However, when penicillin was injected intramuscularly, the skin of the face did not react but the hands and feet became involved with edema and a confluent papular eruption. The skin of the feet had never been previously exposed to penicillin but had been the seat of a chronic dermatophytosis.

SUMMARY

With the report of our case 1, we place on record the second case of proved contact dermatitis due to penicillin, the first having been reported by Pyle and Rattner.[1] If epidermal sensitivity was present in case 2, we were unable to confirm it by contact and intradermal tests. The reaction finally obtained on deep intramuscular injection was that of the disturbance of the fungus antigen relationship first reported by Graves, Carpenter and Unangst. This reaction seems to occur in patients who have had a focus of dermatophytosis on the feet. The short interval between the injection of penicillin and the reaction on the hands and feet is suggestive of the Jarisch-Herxheimer reaction, but this possibility is ruled out because of the lack of evidence that penicillin is a fungicide and because the cutaneous reaction persisted as a subacute inflammatory reaction for seven days.

Clinical Notes

MUTILATING FORM OF AMERICAN LEISHMANIASIS

Oswaldo G. Costa, M.D., Bello Horizonte, Brazil

Assistant in Clinic of Syphilis and Skin Diseases of the Faculty of Medicine, University of Minas Geraes

American leishmaniasis may cause serious deformities which need to be remedied by plastic surgery. My case is a striking example of extensive mutilation caused by the long-continued disease, due to the patient's carelessness with regard to treatment and possibly also to the development of resistance to treatment. The negative results of microscopic search for leishmanias do not nullify the diagnosis, as the duration of the eruption was extremely long and as the patient was treated again and again. When the disease is of long duration, it is much more difficult to find the parasite than when

Fig. 1.—Congenital syphilis (patient of Dr. Orsini de Castro).

the onset is recent. In inveterate cases, the specificity of the process diminishes according to the law of Levandowsky and Jadassohn. In diagnosis, the disease must be differentiated from syphilis (fig. 1), leprosy and lupus.

REPORT OF A CASE

J. A., a white Brazilian farmer, lived at Uberlandia. The family history showed nothing worthy of note, except that he has a brother who also suffers fr American leishmaniasis. The patient stated that wh he was 3 months old there appeared on the left side his face a small itchy papule which ulcerated an progressed until it reached the size of a walnut. physician was consulted, who treated the disease su cessfully. After a time the same condition was notic in one of his nostrils. Since then, the eruption ha had periods of regression due to treatment; but it alway recurred, for he has not been assiduous in continuin the treatment.

General physicial examination showed nothing ab normal. Dermatologic examination showed destructio of the entire cartilage of the nasal pyramid and also o

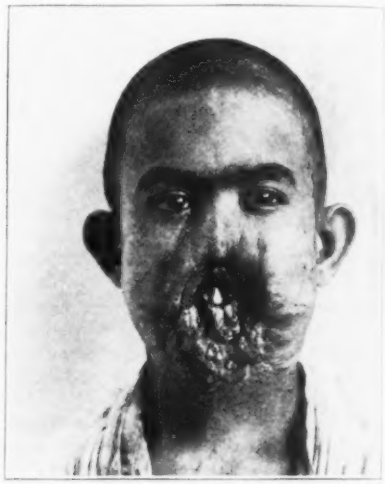

Fig. 2.—Mutilating form of American leishmaniasis.

the upper and the lower lip. All around the buccal orifice there was a secreting ulcer with red granular floor and a nonelevated border. The orifice of the mouth was circular, and its movements were impeded by the formation of scars. The teeth were irregular and some of them had been extracted. The skin around the ulcer was cyanotic. The buccal cavity was unaffected (fig. 2).

The Wassermann and Kahn reactions of the blood were negative. Microscopic search for leishmania was unsuccessful.

Rua Ceará, 1695.

CONTACT DERMATITIS FROM AMORPHOUS SODIUM PENICILLIN

Seymour H. Silvers, M.D., Brooklyn

T. G., a chemist aged 36 years, has during the past two years conducted extensive research on the chemistry of penicillin. He first consulted me in December 1943, because of an itchy rash on the eyelids and on the penis of three months' duration. The eruption appeared approximately one year after he had begun the work on penicillin. He was treated symptomatically with soothing applications, and it was noted that whenever he avoided direct contact with penicillin the rash improved or disappeared entirely.

Examination showed red, swollen eyelids. The conjunctiva was red. The skin adjacent to the eyelids showed an ill defined, red, pinhead-sized vesiculopapular early eruption. The penis was red and edematous and showed a discrete, papulovesicular rash. There were no lesions on the fingers and hands.

A patch test on the right arm with a solution made of the yellow amorphous sodium penicillin which is used in the therapy of infections had to be removed after twenty-seven hours because of burning and itching. After seventy-two hours, the site of the patch test still showed a pinhead-sized vesicular rash on a red, edematous base. The result of a patch test with a solution of pure white crystalline sodium penicillin recently prepared was negative.

COMMENT

The yellow amorphous sodium penicillin contains about 65 per cent of pure crystalline sodium penicillin. The remainder consists of impurities such as pigments, other forms of penicillin and unknown factors. This patient reacted only to the "impure" sodium penicillin. It is therefore reasonable to assume that the "impurities" present in sodium penicillin were responsible for the contact dermatitis.

Pyle and Rattner [1] reported a case of dermatitis due to penicillin. The clinical picture of the rash presented by their patient resembled closely that of this patient. However, they obtained a positive reaction to a patch test with a crystalline penicillin material. My patient's skin reacted only to the "impure" yellow amorphous sodium penicillin.

SUMMARY

A chemist working with penicillin was observed to have contact dermatitis. Patch tests showed that the patient's skin reacted only to the "impure" sodium penicillin. Pure white crystalline sodium penicillin produced no reaction in the skin. It is therefore reasonable to assume that the contact dermatitis in this patient was caused by the "impurities" present in the available yellow amorphous form of sodium penicillin.

920 Bushwick Avenue.

1. Pyle, H. D., and Rattner, H.: Contact Dermatitis from Penicillin, J. A. M. A. **125**:903 (July 29) 1944.

Correspondence

SCLERODERMA WITH BULLAE

To the Editor:—In a recent article "Bullous Lichen Sclerosus et Atrophicus" (ARCH. DERMAT. & SYPH. **49**:423 [June] 1944), Dr. C. Russell Anderson discussed rather extensively my article "Localized Scleroderma with Bullae" (ARCH. DERMAT. & SYPH. **43**:361 [Feb.] 1941) and came to the conclusion that my case was one of bullous lichen sclerosus et atrophicus rather than scleroderma with bullae.

Unfortunately, Dr. Anderson had not had the opportunity of seeing my patient. She had been twice presented before the San Francisco Dermatological Society, and the diagnosis had been accepted by the majority of the members present. The main question in the members' minds was not in regard to the diagnosis of scleroderma but rather in regard to the mechanism of productions of the bullae—whether they were factitious or were due to friction or to drugs. Dr. Howard Morrow saw her in consultation and agreed with the clinical diagnosis.

Several of our members felt that the histopathologic changes were compatible with the clinical diagnosis. One member did not agree but offered no other diagnosis. The more I see of dermatopathologic conditions, the less dogmatic I become. For I am certain that there are many variants from typical microscopic pictures—in fact, just as many as there are variants in the clinical appearance of the lesions.

So it seems to me that the opinions of experienced dermatologists who saw both the patient and the histologic preparations should be given weighty consideration in favor of the diagnosis of localized scleroderma with bullae.

H. J. TEMPLETON, M.D., Oakland, Calif.

LOCAL PENICILLIN THERAPY

To the Editor:—In the September issue of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY there is a short note by Dr. Schoch on the local use of penicillin. I have not used penicillin in the fashion Dr. Schoch has, and, while I have no doubt of the accuracy of his observations, I should like to sound a note of caution which I hope ultimately will prove unnecessary to be needed. In a paper just read before the American Public Health Association, Dr. Welch and I have shown that repeated intradermal injections of penicillin at five day intervals sensitized 9 out of 9 persons. The majority of the reactions were of the Arthus type. While none of the reactions were severe, this may have been because when the reactions became manifest we did not continue with further injections. What effect such a sensitization would have on the therapeutic use of the drug is unknown.

I realize, of course, that Dr. Schoch's technic and ours differed considerably, but on theoretic grounds there may be an analogy, inasmuch as we believe that the reason we got so many sensitizations with the technic used was the rate of excretion of the penicillin and it would appear not too unlikely that when penicillin is used as Dr. Schoch has suggested the rate of excretion may be similar.

The purpose of this letter is to suggest that when penicillin is used locally it be used with caution and with an eye kept open for possible sensitizations or a similar sequence of events may be again experienced as was had with the topical use of the sulfonamide compounds.

ADOLPH ROSTENBERG JR., M.D.,
Washington, D. C.

RAT MITE DERMATITIS

To the Editor:—I regret that in writing the article "Rat Mite Dermatitis" (ARCH. DERMAT. & SYPH. **50**: 90 [Aug.] 1944), I overlooked the article by Dr. E. K. Stratton, "Rat Mite Dermatitis" (*California & West. Med.* **51**:391 [Dec.] 1939).

I should like to add that where rat mite infestation is suspected, but the mites are difficult to find, judicious placing of flypaper about the room or rooms for forty-eight hours will frequently entrap them. This device was resorted to by a patient of mine, with success.

C. RUSSELL ANDERSON, M.D., Los Angeles.

News and Comment

NOTICE

Dr. Roger Denis Baker, associate professor of pathology in charge of surgical pathology, Duke University School of Medicine, has been appointed professor and chairman of the department of pathology in the Medical College of Alabama at Birmingham, a division of the University of Alabama. He will move to Birmingham on Dec. 1, 1944. Dr. Baker requests that autopsy and surgical materials for the Fungus Disease Registry be sent to him at Birmingham 5, Ala., after that date. The mycologic and serologic materials of this Registry should continue to be sent to the office of Dr. David F. Smith, Duke Hospital, Durham, N. C.

DEATHS

Dr. John Harper Blaisdell died suddenly on Oct. 25, 1944.

Obituaries

JEROME KINGSBURY, M.D.
1871-1944

Jerome Kingsbury died on July 15, 1944, of a cerebral hemorrhage, at the New York Polyclinic Hospital, where he had served as visiting dermatologist since 1925.

Dr. Kingsbury was born in Boston. His father was Alden N. Kingsbury and his mother Mary Jerome Kingsbury. He graduated from Bellevue Hospital Medical College in 1897, was an intern at the New York Skin and Cancer Hospital from 1898 to 1900 and in 1901 began a long and faithful service at the Skin and Cancer Hospital, first as clinical assistant and later as attending physician, which service he terminated in 1920. In 1929 he accepted a reappointment as attending physician and remained until the amalgamation of the New York Skin and Cancer Hospital and the New York Post-Graduate Medical School and Hospital on Sept. 1, 1934, when he resigned. In his last year of service he was elected president of the medical board.

JEROME KINGSBURY, M.D.
1871-1944

Dr. Kingsbury was visiting dermatologist at the City Hospital from 1920 to 1936, where he became expert in the diagnosis of leprosy. He was chief of the department of dermatology at the Presbyterian Hospital Dispensary from

1900 to 1917. At the time of his death, he was attending dermatologist to the Midtown Hospital, consulting dermatologist to the City Hospital and to the Harlem Eye and Ear Hospital and a trustee of the Northern Dispensary. He had served as one of the professors of dermatology and syphilology at the New York Polyclinic Medical School and Hospital since 1925.

Dr. Kingsbury wrote the text of a "Portfolio of Dermochromes" published by Rebman, New York, 1913, containing the colored plates which appeared in the fourth edition of Jacobi's Atlas. The text was entirely new and clearly presented the American viewpoint of dermatology at that time.

He was elected a member of the New York Dermatological Society in November 1908 and of the American Dermatological Association in 1913. He was also a member of the Manhattan Dermatological Society and a fellow of the American Medical Association, the American Academy of Dermatology and Syphilology and the New York Academy of Medicine. He served as chairman of the section of dermatology and syphilology of both the Medical Society of the State of New York and the New York Academy of Medicine.

An outstanding characteristic of Dr. Kingsbury was an extraordinary degree of reticence, which was manifested professionally but not socially. Because of it, he rarely entered into dermatologic discussions at the societies of which he was a member.

Dr. Kingsbury's modesty and droll humor were shown by the following incident. Two of his colleagues were attending a moving picture show, where on the screen to their surprise they saw Jerome Kingsbury entering a balloon, to take part in an international contest. One of them later said to him, "Why didn't you tell us you were a balloonist?" to which Kingsbury answered, "Why, you never asked me." He was a man who for many years had been a licensed balloon pilot, a charter member of the American Institute of Aeronautical Engineers, chairman of the balloon committee of the Aero Club of America, a member of the Early Birds and a competitor in many national and international balloon races for years, who was so modest that, despite their frequent association with him, he never spoke to his friends of his exploits. Dr. Kingsbury was also a life member of the United States Revolver Association and had won many cups for his expert marksmanship.

Dr. Kingsbury's interest in military affairs began when he served as a member of the Seventh Regiment, New York National Guard. In 1915, he attended the first Plattsburg officers' training camp. During the first World War he served as captain in the Medical Corps in France, and after the war he held the rank of colonel in the Medical Reserve Corps. He had served as a commander of the Military Society of the War in 1812 and was surgeon of the Veteran Artillery Corps and the New York City Patrol Corps.

His death creates a great void in the hearts of those of us who were fond of him. It is hard to say farewell after thirty-two years of agreeable professional association.

PAUL E. BECHET, M.D.

ANDREW PORTER BIDDLE, M.D.

1862-1944

Dr. Biddle was born in Detroit, Feb. 25, 1862, the son of William Shepherd Biddle and Susan Ogden Biddle. In his early life he received his education in various parts of the world, including Geneva, Switzerland, and Heidelberg, Germany, completing his school work in the Detroit High School in 1880.

He naturally turned to the military service, as other members of his family had done, and spent three years at the United States Naval Academy, at Annapolis, Md. On leaving Annapolis he decided to study medicine, entering the Detroit College of Medicine in the same year and being graduated in 1886. After an internship at Harper Hospital he took postgraduate work in Leipzig, Germany, in 1891.

Even in his early years he was interested in education and began the teaching of dermatology in the Detroit College of Medicine in 1892 and continued in the department until 1918, when he became professor emeritus of dermatology. Although Dr. Biddle was not a prolific writer, he wrote on current topics and in other ways influenced medicine and dermatology by stimulating the younger men by example and encouragement.

The offices which he held are numerous, having been president of the Michigan State Medical Society, of the Wayne County Medical Society, and of the Detroit Dermatological Society. He also served as president of the American Dermatological Association in 1926 at the Philadelphia meeting on the occasion of its fiftieth anniversary. He took pride in the fact that he had never missed a meeting of that organization unless prevented by illness.

During his long medical career, of fifty-seven years, he served on the staffs of various hospitals in Detroit, served the Detroit and the Michigan Board of Health in various capacities and was a member of many local state and national societies. He was also one of the oldest members of the Detroit Academy of Medicine, being elected in 1887 and being its president in 1912.

The Michigan State Medical Society instituted the Andrew P. Biddle Oration in recognition of his long, loyal and continuous service. His devotion to the advancement of education and ethics in the medical profession was recognized also by the University of Michigan in granting Dr. Biddle the honorary degree of Master of Arts in 1935. The honorary degree of Doctor of Science was conferred on him in 1929 by the College of the City of Detroit.

In 1936 a dinner was given to Dr. Biddle by the Wayne County Medical Society as an expression of the honor and esteem in which he was held by the medical profession of Detroit.

In addition to all his medical activities, Dr. Biddle found time to serve in civic offices and for many years was a member of the library commission and of the board of education of Detroit, also serving as president in each group at various times.

During the Spanish American War in 1898, the military spirit again prevailed and he joined the Thirty-First Michigan Volunteer Infantry as a surgeon with the rank of major.

In 1892 Dr. Biddle married Grace Wilkins, and one daughter was born to this marriage.

ANDREW PORTER BIDDLE, M.D.
1862-1944

This daughter's death a few years ago was keenly felt by Dr. Biddle, and shortly after that his health began to fail. The death of his wife within the past few years left Dr. Biddle much alone, but he continued his work even when he should have rested on his laurels.

Andrew Porter Biddle will live long in the hearts and memories of those who knew him, whether laymen or physicians, as he was one of the few about whom it may be said, "He never had made an unkind remark about anyone." If he could not say words of praise, he was silent; and at all times he was a perfect gentleman and a wonderful friend. His death will be mourned by untold thousands, but his memory will be ever fresh.

ROBERT C. JAMIESON, M.D.

Abstracts from Current Literature

EDITED BY DR. HERBERT RATTNER

A NOTE ON THE SO-CALLED UNDIFFERENTIATED AND EMBRYONIC CELLS. PETER GRUENWALD, Arch. Path. **36**:190 (Aug.) 1943.

"Undifferentiated" and "embryonic" cells as described in the literature of pathology and histology are discussed on the basis of modern developmental physiology. It is found that most of the concepts in question are based on the old idea that only undifferentiated or embryonic cells can be credited with possessing latent developmental potencies. It is known now that such potencies may be present in differentiated cells of the adult organism as well, and that their presence is not correlated with morphologic characteristics. Much confusion has been created by the use of morphologic terms to indicate the state of potencies in a cell or tissue. This procedure is misleading and should be abolished in favor of terms and concepts based on developmental physiology.

AUTHOR'S SUMMARY.

TRENCH FOOT. Editorial, Bull. U. S. Army M. Dept. March 1944, no. 74, p. 46.

Trench foot, immersion foot and frostbite are related conditions resulting from exposure to wet and cold. In the Kiska campaign immersion foot and trench foot comprised about 10 per cent of the total injuries and diseases; in the Attu campaign 93 patients with trench foot required admission to the hospital. Trench foot occurs as a result of prolonged exposure to wet and cold, contributing factors being tight footgear, immobility and dependency, which reduce peripheral circulation. Prevention is of paramount importance.

The principles of treatment consist essentially of rest, avoidance of local trauma and infection, elevation of the feet to promote drainage of edema fluid and reduction of metabolism in the infected parts. The period of rest in bed is determined by the degree and rate of subsidence of edema and circulatory disturbances. Measures to prevent secondary infection, including use of antitetanus serum, should always be instituted, and in case of threatened infection use of sulfadiazine by mouth is recommended.

TREATMENT OF BURNS DUE TO CHEMICAL WARFARE AGENTS. S. S. SCHERLING, B. M. OVERHOLT and K. H. STAHMER, Bull. U. S. Army M. Dept., March 1944, no. 74, p. 52.

The authors report their clinical experiences in treating 95 burns of the skin caused by chemical warfare agents which were serious enough to warrant hospitalization. The agents producing the burns were mustard gas, lewisite gas, white phosphorus and arsenic trichloride.

Ninety-five per cent of the patients with burns due to mustard gas did not realize that they had been burned until from six to twenty-four hours later. The first indication of such a burn was pruritus and erythema followed by pain about the contaminated area. Within eight to twenty hours, there was a doughnut-shaped vesicle filled with clear fluid, surrounded by a zone of erythema. First aid given within the first five minutes may prevent the burn entirely or red its degree. The recommended procedure for first a is as follows: The clothing must be removed; excess mustard gas is blotted off with tissue; M ointment (protective ointment M-4, chemical warfa issue) is applied and washed off immediately, af this a soap and water shower is taken and M-4 oi ment is reapplied and then the shower is repeate Once the vesicant lesion was formed locally, definit treatment included: (1) pressure dressing; (2) sulf diazine-triethanolamine spray; (3) applications of va ous ointments; (4) amyl salicylate dressings, and (saline baths. The authors found the most successf form of management to be débridement and applicati of pressure dressings wherever possible.

In burns due to lewisite gas, erythema develops ra idly and vesicle formation is usually complete in twel hours. The vesicle is well defined, overlies the enti erythematous area and is filled with an opaque flu containing traces of arsenic. The treatment is esse tially the same as for mustard gas burn.

The first aid treatment of burns due to white pho phorus consists of immediate immersion of the burn part in water, followed by the application of 1 to per cent solution of copper sulfate. The late treatme is the same as that for mustard gas burns. The fir aid and later treatment of nitrogen-mustard gas burn is the same as for those due to mustard gas, and th same is recommended for burns from arsenic trichlorid

The authors stress that pressure dressings are th method of choice in the local treatment of deep burns The one exception is extensive lewisite burns, for whic baths or dressings of saline solution are recommende

TREATMENT OF SKIN INFECTIONS IN THE ASSAM BURMA JUNGLE. JOHN H. GRINDLAY, Bull. U. S Army M. Dept., March 1944, no. 74, p. 74.

The author discusses minor infections of the skin fo which he used magnesium sulfate, a 50 per cent solu tion in pure glycerin, as wet dressings. Among th major infections he discusses the tropical ulcer, o Naga sore. Naga sores are seen most frequently i patients with systemic diseases, especially chronic ma laria, but Grindlay does not believe that there is any direct connection between the two diseases. He does, however, believe that Naga sore is related to beriberi. Supporting this contention is the fact that brewers' yeast or thiamine hydrochloride help to heal the Naga sores.

Smears made from active portions of the ulcer show a predominance of fusiform spirochetes identical with Vincent's organism. The lesion begins as a minute abrasion, friction blister or insect bite, most commonly a leech bite. The earliest lesion is a yellow superficial bleb filled with puriform exudate; at the center of the skin underlying the bleb is usually a minute puncture hole. Transition from the early acute to the acute fulminating lesion occurs in two or three days. The fulminating lesion is an extremely painful ulcer.

For the treatment of the early acute lesion the author commends trimming of the blister and application of magnesium sulfate and glycerin dressings. The fulminating ulcer is débrided, and sulfanilamide (powder or crystals) is rubbed into all surgically exposed tissues, after which all the wounds are packed with petrolatum gauze. After the entire limb has been wrapped in a layer of cotton, a plaster of paris cast is applied. Systemic diseases, such as malaria and dysentery, should be treated simultaneously with the ulcer.

STRAKOSCH, Chicago.

THE ABSORPTION, EXCRETION AND DISTRIBUTION OF PENICILLIN. CHARLES H. RAMMELKAMP and CHESTER S. KEEFER, J. Clin. Investigation **22**:425 (May) 1943.

Data are presented concerning the blood concentration and urinary excretion of penicillin after the administration of 5,000 to 40,000 Florey units by several routes.

Intravenous injection of penicillin resulted in high initial concentration in the blood plasma, which was followed by an abrupt fall. Traces of penicillin were found in the blood for thirty to two hundred and ten minutes after the injection, the length of time depending on the amount administered. The sharp fall noted in the serum concentration immediately after injection was associated with an increased excretion in the urine. The average excretion after intravenous injection was 60 per cent of the administered dose.

Penicillin was rapidly absorbed when given intramuscularly and slowly absorbed after subcutaneous injections. Excretion in the urine was rapid following intramuscular injections and delayed after subcutaneous injections.

Absorption from the body cavities was delayed, and this was reflected in the slow excretion of penicillin by the kidneys. The total amount found in the urine was somewhat lower than that obtained following intravenous injection. Fluid aspirated from the pleural and joint cavities, twenty-two and thirteen hours after the injection, showed appreciable amounts of penicillin remaining.

Administration of penicillin by enteral routes showed that absorption from the duodenum was rapid, whereas oral and rectal doses were poorly absorbed. These findings may be explained by the inactivating effect of penicillin of acid and Escherichia coli. After oral, intraduodenal and rectal administration, the average amount excreted in the urine was extremely small.

In the presence of renal failure, penicillin was not excreted rapidly, and as a result, high concentrations were maintained in the blood stream after intravenous injections.

Studies on the distribution of penicillin showed that the substance failed to penetrate the red cells in significant amounts. In general, the average concentration found in the erythrocytes was less than 10 per cent of the concentration in the plasma. No penicillin was found in the spinal fluid, saliva or tears in subjects receiving it intravenously.

[AUTHORS' SUMMARY.] [AM. J. DIS. CHILD.]

NOTES ON MILITARY DERMATOLOGY. R. M. B. MACKENNA, Brit. J. Dermat. **56**:1 (Jan.) 1944.

The dermatologic hazards to which the British soldier is exposed are due more to his environment than to his occupation. Of the environmental hazards the following are considered: (1) respirator dermatitis, (2) sensitization to clothing, (3) eruptions caused by sunlight, (4) desert sore, (5) cutaneous diphtheria, (6) cutaneous leishmaniasis, (7) effect of change of climate on diseases to which certain patients are prone and (8) hazards of battle inoculation.

Respirator Dermatitis.—Clinically, respirator dermatitis is manifested as a submental edema, and the incidence varies in accordance with the type of rubber mix and the average duration of intimate contact with it.

Sensitization to Clothing.—A sensitization to woolen textiles has been noted. This sensitivity is of an acquired type and often seems to be provoked by some accident or cutaneous disease. The commonest type is manifested by a persistent localized erythema of the inner aspect of the thighs, but if the condition is provoked by scabies, the eruption produced by further contact with woolen textiles is not localized and may resemble scabies.

Eruptions Caused by Sunlight.—The British army relies on acclimatization and not on the use of antisunburn lotions to protect the skin from the deleterious effects of ultraviolet rays. Acquired hypersensitivity to sunlight after the therapeutic use of sulfonamide compounds has been noted.

Desert Sore.—The "sore" is not primarily a diphtheritic infection but a bullous impetigo. Its importance in the Western Desert can be appreciated when one notes that the incidence in some units was 1 in every 4 or 5 men.

Cutaneous Diphtheria.—Three types of acute diphtheritic infection have occurred (eczematous type, bullous type and cellulitis type) and one chronic type, simulating a chronic infective eczematous dermatitis around the auditory meatus, nostrils or mouth.

Cutaneous Leishmaniasis.—Control of this disease depends on the success of the antifly measures of the authorities responsible for the hygiene of the armies abroad; the incidence has been low.

Effects of Change of Climate on Diseases to Which Certain Patients Are Prone.—Psoriasis does badly in the Middle East generally, worse in Egypt than in Palestine. Desert conditions seem particularly unfavorable. Men who have suffered from seborrheic dermatitis and eczema at home are prone to have a relapse in the hotter countries.

Hazards of Battle Inoculation.—Dermatitis bullosa striata pratensis and vesicant gas burns are considered.

TEXTILE DERMATITIS. J. H. TWISTON DAVIES and A. NEISH BARKER, Brit. J. Dermat. **56**:33 (Feb.) 1944.

The authors report that of 670 admissions to the dermatologic wards of a large military hospital during the first six months of 1943, 110 (16.4 per cent) were for dermatoses proved by patch tests and by the observed effect of resumption of wearing issue clothing to be wholly or partly due to intolerance by the skin of contact with woollen textiles.

The patient usually complains of itching but may report on account of infected excoriations on the legs and thighs. The itching is often worse in the daytime, though it is rare for the patient not to attribute his symptoms to contact with blankets. In general terms it may be said that the signs are seen chiefly, as might be expected, in parts exposed to contact with melton, serge or other woollen clothing. Thus in every case

the lower extremities are attacked with intensity increasing toward the tops of the boots, and in many of them the forearms also. The cutaneous manifestations encountered in order of frequency are (1) prurigo simulating scabies (58 cases), (2) erythematous dermatitis (49 cases), (3) erythema (26 cases), (4) pruritus (18 cases), (5) eczematoid dermatitis (18 cases), (6) facial eczema (10 cases), (7) circumscribed and diffuse lichenification (8 cases), (8) prurigo simplex (4 cases), (9) urticarial eruption (3 cases), (10) acneform eruption (1 case).

Sensitization may occur spontaneously or as the result of friction by garments in association with sweating, but more commonly its onset is determined by some other dermatosis. The supposed determining factor was recorded in only 89 cases. In 54 of these it appears to have been scabies. Arsenical dermatitis accounted for 6. A common experience was for a patient discharged after apparently complete recovery from arsenical dermatitis to return a few days later with a weeping eczema of the scrotum. External irritants (seen mainly in quinine pessary dermatitis and therapeutic accidents) were responsible for 8 cases and infective dermatitis for 10 cases.

Treatment consists primarily in removal of the irritant. The patient sleeps between sheets, has a cotton or linen shirt and wears cotton pajamas by day under his hospital blues. Simple remedies, such as calamine liniment, are no less efficacious than elaborate ones, with which there is always the danger of additional sensitization. It seemed in this series that lapse of time was the most important factor in treatment.

BLUEFARB, Chicago.

HERPES ZOSTER OPHTHALMICUS—TWO RARE MANIFESTATIONS. T. G. WYNNE PARRY and G. C. LASZLO, Brit. J. Ophth. **27**:465 (Oct.) 1943.

A woman aged 52 suddenly became blind in the right eye. Six weeks previously she had had herpes zoster along the course of the right fifth nerve. The diagnosis was acute optic neuritis. Examination of spinal fluid showed 44 small lymphocytes per cubic millimeter and a protein content of 30 mg. per hundred cubic centimeters. Five weeks later vision was gone with an absolute scotoma. The temporal portion of the optic disk showed discoloration.

A man aged 33 had had herpes on his chest six weeks previously. Three weeks later diplopia developed as a result of paresis of the right abducens nerve. The spinal fluid showed an increased cell count, with a high protein content. The paresis cleared.

W. ZENTMAYER. [ARCH. OPHTH.

LIVER EXTRACT IN ARSENICAL INTOLERANCE. K. LAHISI, J. Indian M. A. **12**:141 (Feb.) 1943.

In 23 cases of intolerance to arsenic during treatment for acquired syphilis, the excretion of hippuric acid was increased and the symptoms were improved by daily intramuscular injections of the liver extract. "It is apparent that liver function in arsenical intolerance is improved by the administration of liver."

GONCE, Madison, Wis. [AM. J. DIS. CHILD.

CASE FOR DIAGNOSIS: EPIDERMOLYSIS BULLOSA HEREDITARIA? THERESE KINDLER, Proc. Roy. Soc. Med. **36**:292 (April) 1943.

The patient, a boy 3 years old, had suffered from bullous eruption since fourteen days after his birth. His twin brother had died from a similar disease. Bullae of varied sizes appeared on normal skin, on any part of the surface. The moist axillary and perianal areas showed papillomatous, condyloma-like excrescences. The mucous membranes, nails and hair were unaffected. The blood was normal except for anemia. Various treatments tried by the author are outlined. None had any effect.

WILLIAMSON, New Orleans. [AM. J. DIS. CHILD.

Society Transactions

CLEVELAND DERMATOLOGICAL SOCIETY

E. W. NETHERTON, M.D., *President*

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May 27, 1943

Case for Diagnosis (Linear Nevus?). Presented by DR. R. E. BARNEY.

Mrs. R. F., a white woman aged 27, states that her ther informed her that he had noticed a dime-sized ed area on the flexor surface of her right wrist at th. This area had increased in size, gradually exding up the arm.

Involving the flexor surface of the right wrist, chiefly the ulnar aspect, is an area half the size of a palm which the skin shows a noninflammatory stippling. e process extends up the ulnar aspect of the forearm a ½ inch (1 cm.) band to the junction of the middle d upper thirds.

A biopsy specimen taken from the area on the wrist wed a moderate degree of hyperkeratosis, with tening of the rete pegs. There was atrophy of the illary layer of the corium and moderate fibrosis of reticular layer.

DISCUSSION

DR. H. N. COLE: This may be an example of one the localized ectodermal dysplasias, there being ugh tissue broken at birth, with scar formation, to se the picture seen here. Often the marks are mmetric, but not always. The asymmetric ones are ally but not always found on the scalp, and I think t would explain this picture.

DR. J. R. DRIVER: How would you explain the read?

DR. H. N. COLE: I just saw one lesion.

DR. R. E. BARNEY: It has spread since birth. It as originally small, but now the same change goes the ulnar aspect of the arm.

DR. E. J. ARDAY: Is there not a possibility that this healed morphea? There is a considerable amount of arrangement of collagenous tissue in the section I amined.

emphigus Foliaceus. Presented by DR. R. E. BARNEY.

M. F., an Italian woman aged 58, noticed several all itching blisters on the knees and back in October 42. The eruption gradually spread, and in two months e entire body was involved. At times the skin uld be peeled off in strips, and at intervals new ps of blisters would appear while others would sappear. She had lost 100 pounds (45.4 Kg.) in ht months. Itching has been a prominent symptom. times she has been so weak she could not walk. er physician gave her seven intramuscular injections bismarsen and thirty intramuscular injections of tamins, with little improvement.

When seen on March 12, 1943 she appeared fairly ell nourished and not acutely ill. The entire cutaneous surface was reddish brown and presented universal scaling. The scales varied in size from that of a pinhead to that of a quarter. There were pinhead-sized to glass pinhead-sized pustules and vesicles scattered here and there. The palms were deeply fissured. The legs were swollen and firm to palpation. Nikolsky's sign was elicited.

Treatment has consisted of colloidal baths and soothing keratolytic ointments locally. She has been given large doses of vitamin D (300,000 U. S. P. units daily) with no improvement. Subsequently, sulfathiazole was administered, and after one week there was an exacerbation of the eruption characterized by a generalized bullous dermatitis and an elevation of temperature to 40.5 C. (104.9 F.). The symptoms rapidly subsided when use of the drug was discontinued. She has received transfusions of whole blood and blood plasma. On May 1, 1943 intravenous injections of germanin were started and to date she has received 6.5 Gm., with some improvement in the eruption and in her general condition.

The Kline reaction of the blood was negative. The hemogram revealed 4,120,000 red blood cells and 11,500 white blood cells per cubic millimeter. The hemoglobin amounted to 12.6 Gm. per hundred cubic centimeters. The differential blood count showed 51 per cent neutrophils, 17 per cent lymphocytes, 9 per cent mononuclear leukocytes, 21 per cent eosinophils and 2 per cent basophils. The blood level of urea nitrogen was 8.1 mg. per hundred cubic centimeters, and the plasma level of sodium chloride was 610 mg. per hundred cubic centimeters. The blood pressure readings were within normal limits.

A biopsy was performed on May 20, 1943 on a specimen from the right side of the abdomen and showed bullous formation in the stratum corneum. There was parakeratosis. The cells of the epidermis revealed intracellular and extracellular edema, vacuolation and some mitotic figures. There was an infiltrate in the papillary layer of the corium made up of lymphocytes, polymorphonuclear leukocytes and numerous chromatophores. The infiltrate was greatest beneath the bullae.

DISCUSSION

DR. B. F. BARNEY, Columbus, Ohio: I favor a diagnosis of dermatitis herpetiformis. From the extent of the eruption one would expect considerable prostration, while actually the patient seems to be in perfect health. I believe that a trial intramuscular injection of an arsenical followed by an arsenic preparation by mouth would be advisable.

DR. C. L. CUMMER: There was much pigmentation present, suggesting the possibility of dermatitis herpetiformis. Again, one would have to consider that this pigmentation has resulted from the ingestion of arsenic.

DR. R. E. BARNEY: Drs. Cole and Driver saw this patient early in the course of the disease. They thought it was a Senear-Usher type of pemphigus. The eruption was spotty at that time and not as nearly universal as now.

DR. E. W. NETHERTON: I favor the diagnosis of pemphigus foliaceus. This patient has a generalized erythroderma, and there are moist areas as well as thin loosely adherent crusts scattered over the trunk.

Such an extensive involvement of the skin does not occur in dermatitis herpetiformis; there should be at least a few areas of normal skin even in the most severe outbreak of dermatitis herpetiformis.

DR. R. E. BARNEY: The pigmentation was present when I first saw the patient. She has not responded well to any therapy so far employed. I think that it might be well, in view of the fact that she has not had much arsenical therapy, to try the Davis method of treatment (administration of ferric cacodylate and a thromboplastic substance). Germanin produced a slight improvement.

A Case for Diagnosis. Presented by DR. R. E. BARNEY.

P. W., a girl aged 9 years, noticed a small red itching macule on the inner aspect of the right leg in June 1942. This gradually increased in size and turned brown in about four months. In October of the same year other lesions appeared one after the other. Except for the usual childhood diseases there have been no serious illnesses. She has not lost weight. A tuberculin patch test in March elicited a negative reaction.

Involving the upper half of the inner aspect of the right leg are eight pea-sized to quarter-sized lesions. These vary from dark red to deep brown. They are covered with a slight scale and are only slightly infiltrated. A lesion on the inner aspect of the calf is the size of a quarter and made up of slightly elevated papules of the size of a small pea. This lesion appeared last and is the one from which a specimen was removed for biopsy. The borders of some of the lesions show telangiectases.

The hemogram showed a relative lymphocytosis.

Histologic examination revealed slight hyperkeratosis. There was a sharply defined infiltrate in the papillary layer of the corium made up of lymphocytes, plasma cells and fibroblasts.

DISCUSSION

DR. H. N. COLE: I thought of a fixed drug eruption.

DR. J. R. DRIVER: I looked at the slide, and it looked to me like lichen planus. There was a cellular infiltrate in the papillary layer of the corium. Histologically it looked like lichen planus, but clinically the eruption is only suggestive of this disease.

DR. E. W. NETHERTON: I thought that the histologic changes were suggestive of lichen planus and also that a clinical diagnosis of lichen planus was justifiable. I have seen the same kind of lesions associated with typical papules of lichen planus. The lesions of this patient are annular, shiny and brownish red. The location is not unusual for lichen planus, a disease which is prone to have bizarre clinical manifestations. An interesting feature is the hemogram. The patient has a relative lymphocytosis.

DR. H. G. MISKJIAN: I do not think that histologically this can be called a case of lichen planus just because there is an inflammatory infiltrate in the superficial layers of the corium. The cells of the malpighian layer of the epidermis are normal, not swollen and cloudy, and the hypertrophy of the interpapillary pegs is not the same as in lichen planus. The epidermis is not particularly hyperplastic. There is no hypergranulosis. The most important point against lichen planus is the composition of the cellular infiltrate in the corium, in which the number of lymphocytes is probably not more than 50 per cent. All the rest are histiocytes, polymorphonuclears and other types of cells. If there had been a few eosinophils, it would be possible to think of mycosis fungoides. I do not know what this is. It is an interesting and unusual eruption, histologically, I feel sure, it is not a lichen planus.

DR. E. W. NETHERTON: There may be a p morphonuclear infiltrate in lichen planus.

DR. H. G. MISKJIAN: My impression is that sees mostly lymphocytes.

DR. C. L. CUMMER: I am inclined to view significance of the blood count with skepticism, a think children are apt to have high lymphocyte co I think it would be wise to check this at a later

DR. E. W. NETHERTON: Is there a history of recent illnesses?

DR. R. E. BARNEY: Other than usual childh diseases there have been no serious illnesses. I th the clearcut infiltration in the papillary area is s gestive of lichen planus, but I do not believe that lymphocytic element is predominant enough to fit with that picture. It is more of the nature of productive infiltration. From the histologic obser tions and the relative lymphocytosis in the hemogra the possibility of a lymphoblastoma suggests itself.

Pyoderma Gangrenosum. Presented by DR. R. BARNEY.

R. B., a white man aged 24, has had three attacks ulcerative colitis since December 1940. Accompany the second attack, he had "boils" on the poster surface of the right thigh, the right buttock and great toe. These lasted about three days. The

Pyoderma gangrenosum.

attack of colitis began on March 1, 1943. On Mar 27, while he was in the hospital, a lemon-sized painf swelling appeared over the lateral aspect of the le arm. About 10 cc. of pus was aspirated from this lesio It recurred in three days and healed after incision an drainage. Shortly afterward two similar but small lesions appeared on the lateral aspect of the right arm These healed in five days after aspiration, incision an drainage. At about the same time a small "pimple developed on the outer surface of the right leg at th junction of the middle and lower thirds. This lesio increased in size and about five days later it discharge

s and a palm-sized area of skin sloughed off, leaving ulcer. Within a week two similar lesions appeared the anterior surface of the right leg and one on the t leg. There has been little pain.

The colitis was controlled in three weeks. After a ek the ulcers of the legs began to heal. They were ated with rest in bed, hydrogen peroxide, sulfanil- ide powder and irradiation from an infra-red lamp. ter ointment of scarlet red was applied.

The patient is a fairly well nourished, well developed an. Involving the lateral aspect of the right leg at junction of the middle and lower thirds is a sub- tely inflammatory purplish vegetating ulcer 2½ hes (6.4 cm.) in diameter. The base is bathed with seropurulent discharge, while the border shows idence of healing. Just below the right knee is an al scar 5 by 3 cm., presenting a few pea-sized ulcer- ed areas. Below this is a palm-sized scar. On the terolateral aspect of the left leg about its middle is scar 8 by 4 cm., in the center of which is an ulcer cm. in diameter, with an arcuate border and a purplish se covered with a serous discharge. On the lateral pect of the left arm is a scar 2.5 cm. in diameter, in e center of which is a sinus draining a serous material.

The Kline reaction of the blood was negative. Culture the pus yielded Staphylococcus albus. The urinalysis ve normal results. A hemogram showed 3,850,000 thrócytes and 46,050 leukocytes per cubic millimeter. he temperature at this time was 38.8 C. (101.8 F.). he differential blood count showed 79 per cent neutro- ils, 16 per cent lymphocytes, 3 per cent eosinophils d 2 per cent metamyelocytes.

DISCUSSION

DR. H. J. PARKHURST, Toledo, Ohio: There is mething bizarre about the appearance of the lesions, d I feel, in view of the patient's age, 24, that one ill have to entertain the possibility of dermatitis ctitia.

DR. H. N. COLE: I think that one should rule out e possibility that this is a bromoderma. There are ngating sharply defined lesions on the shins. I did t notice anything in the history of a search being ade for bromides in the urine. I am somewhat clined to agree with Dr. Parkhurst that there is a ggestion of a factitial process.

DR. J. A. GAMMEL: There is a leukocyte count re- orded of over 40,000. Was that repeated?

DR. R. E. BARNEY: When the leukocyte count was erformed, the patient had an elevation of temperature. Several counts were made with essentially the same esult.

DR. E. C. STERN: I have the same impression as Dr. Parkhurst. One sees that the lesions on both arms healed after incision, leaving a small scar without be- coming gangrenous. The ulcerations on the legs are of a different type. They are deep, sluggish, gangrenous ulcers with sharply defined borders and little or no inflammatory reaction of the surrounding tissue.

DR. H. A. HAYNES JR., Akron, Ohio: I do not believe that this is a case of pyoderma gangrenosum because the areas are not undermined and rarely does one see hypertrophic granulation tissue built up as with these lesions. There is an associated colitis, and I wonder whether the patient may have amebiasis cutis.

DR. R. E. BARNEY: Against the possibility that this is a dermatitis factitia is the fact that the lesions developed while the patient was in the hospital under observation. The first lesion was on the arm and appeared as an abscess, which was aspirated and from which 10 cc. of pus was obtained. The patient certainly could not produce an abscess. That lesion healed after it was incised, and a small scar remained. Lesions developed on the other arm, which responded to the same type of treatment. The lesions on the legs appeared rapidly as abscesses, and in a short time the tops sloughed off, leaving clearcut ulcers. He says that he has not taken bromides, but that does not entirely rule out the possibility. I think this is a typical case of pyoderma gangrenosum.

DR. J. R. DRIVER: Was any search made for amebas in the lesions? If amebiasis cutis can be ruled out, I favor a diagnosis of ulceration of the skin due to ulcerative colitis. Cases of this kind have been reported.

DR. R. E. BARNEY: Amebas were not found.

Epitheliomatosis; Arsenical Keratosis; Psoriasis. Presented by DR. R. E. BARNEY.

A. S. N., a white man aged 46, states that he has had psoriasis for thirty-seven years. Ten years ago the lesion on the right side of the trunk was first noticed, beginning in a patch of psoriasis. About eight months ago a granulating "lump" appeared in the center of this patch. Twenty years ago a physician prescribed "black pills" for psoriasis. He took these intermittently for six months. A year later an eruption appeared on the palms and soles.

The patient is a well nourished, well developed blond man, who has psoriasis of the scalp, neck, elbows and legs. The palms and soles revealed translucent keratotic papules from the size of a pinhead to that of a small pea. In addition, on the trunk and extremities are numerous yellowish brown keratotic papules of similar size. Involving the right side of the chest, about 15 cm. below the axilla, is a 5.5 by 3 cm., roughly oval scaly patch with a fine threadlike border. In its center is a cherry-sized translucent granulating nodule. This lesion bleeds easily on manipulation. There is an atrophic scaly patch 2.5 cm. in diameter, somewhat similar to the one just described, on the upper portion of the back about 10 cm. to the right of the seventh cervical vertebra. There is a pea-sized erosion on the left side of the scrotum.

The patient had been treated for a sore throat off and on for the past seven months. One month ago difficulty in swallowing developed.

A specimen for biopsy was removed from the lower border of the patch on the right side of the trunk so as to include normal skin, the threadlike border and the granulating nodule. The epidermis showed a moderate degree of hyperkeratosis. There were several areas of characteristic basal cell epitheliomatous degeneration, and at one end of the section there was superficial ulceration. There was an infiltrate in the papillary layer of the corium made up of lymphocytes and plasma cells. It was especially pronounced around the areas of epitheliomatous degeneration. Deeper in the corium there was a perivascular and periglandular infiltration similar to that described.

NOTE.—Esophagoscopy on June 10, 1943 revealed a tumor involving the posterior wall of the esophagus extending from the cricopharyngeal constriction downward for a distance of 10 cm. Histologic examination of this tumor revealed a grade III squamous cell epithelioma.

DISCUSSION

DR. J. A. GAMMEL: I have recently seen a similar case which took a rapid course. My patient responded to roentgen therapy for a time. Also a carcinoma

developed in the pectoralis major muscle, which was excised. He died as a result of the carcinoma. He had received arsenical therapy for a period of only six weeks.

DR. H. J. PARKHURST, Toledo, Ohio: I believe that superficial epitheliomatosis occurs chiefly in patients who have had psoriasis for years, and most of them have received arsenic at some time in the course of their disease. I believe it possible that the arsenic may play a part in the development of this epitheliomatosis.

DR. H. A. HAYNES JR. Akron, Ohio: What would Dr. Parkhurst consider a dangerous amount of arsenic in the treatment of psoriasis?

DR. H. J. PARKHURST, Toledo, Ohio: It would vary with the individual patient.

DR. B. F. BARNEY, Columbus, Ohio: This does not occur only in patients with psoriasis. It occurs in other persons. Several years ago I had a patient who had had acne in his youth, and at 40 he still had it. He had epitheliomatosis, and I am sure that others have been seen in which neither psoriasis nor use of arsenic was necessarily precursory.

DR. H. N. COLE: I think that we as physicians should never use the name "Fowler's solution" before the patient. If we use the official name, it will not attract their attention. Just as sure as we use "Fowler's solution," they will remember it, and they will go to a drug store and get it. Often that is what causes the trouble.

DR. E. W. NETHERTON: I think this case demonstrates the difficulties which may arise from the use of inorganic arsenic in the treatment of psoriasis. Psoriasis is a disease which as yet cannot be cured, and I believe that the benefit obtained does not justify the risk of administering arsenic to a patient with it. Cases of this type are not uncommon. It is unfortunate when this unfavorable result of arsenic medication develops.

DR. E. J. ARDAY: I recently removed a 5 by 12 cm. epithelioma from a man's abdomen. It was nodular and deeply ulcerated. I asked the patient, who was an intelligent person, why he had neglected a lesion like this for so long. He stated that his physician had told him many years ago that he had psoriasis and that there was nothing that could be done about it. He thought that this was a lesion of psoriasis.

DR. R. E. BARNEY: I think that the method of choice is excision and that the prognosis is good. As I understand it, the malignant degeneration of arsenical keratosis is of the basal cell type.

DR. E. J. ARDAY: About five years ago I presented a patient with over fifty lesions of multiple epitheliomatosis following psoriasis. One lesion was treated with roentgen rays, and all the rest were treated with solid carbon dioxide, with excellent results.

Recurrent Syphilids Following Five Day Treatment for Seropositive Chancres. Presented by DR. R. E. BARNEY.

A. R., a Negro aged 25, states that two painless sores developed on the penis on March 16, 1943, three weeks after extramarital sexual exposure. He was seen in the differential clinic of St. Luke's Hospital on March 27, at which time a Kline test of the blood elicited a negative reaction. On April 1 he had an indurated, eroded papule of the size of a large pea with a serous discharge at the frenum and a similar lesion in the coronary sulcus on its dorsal surface. Treponema pallidum was demonstrated by dark field examination. There was also a bilateral painless inguinal adenitis. He was sent to the Cleveland City Hospital, where the Kline and Wassermann reactions of the blood were found to be positive and spirochetes were again recovered from the lesions. A lumbar puncture yielded normal fluid. He received 1.2 Gm. of mapharsen by the intravenous drip method in five days. The penile lesions had almost cleared when he finished his treatment but the inguinal adenitis remained. The Wassermann reaction of the blood on April 20, 1943 was strongly positive, but there was no penile lesion. On May 9 two penile lesions developed at the same site as before, and by May 17 there were eight lesions. He was seen again on May 22, when he presented eight glass pinhead–sized to dime–sized, slightly painful, indurated, eroded papules with a serous discharge. These were situated at the frenum in the coronary sulcus and on the under surface of the prepuce. Dark field examination revealed Treponema pallidum. There was a pea-sized to plum-sized, shotty, painless bilateral inguinal adenitis. The trunk presented pea-sized depigmented macules and a sparse glass pinhead–sized inflammatory papular dermatitis. These lesions were not interpreted as syphilitic. There were no lesions in the mouth. The perianal region was clear. The general physical examination revealed nothing abnormal.

His wife had had vaginal bleeding off and on for two years, varying from two weeks to a month. The longest period of freedom from bleeding was two months. She showed a bilateral, painless, pea–sized to olive-sized inguinal adenitis of two weeks' duration. The vaginal examination showed nothing abnormal except bleeding from the cervix. There were indefinite glass pinhead–sized erosions on the left buccal mucosa and left border of the tongue. There was no eruption of the skin. The Kline reaction of the blood was positive.

DISCUSSION

DR. H. N. COLE: This is apparently a true recurrence. These penile lesions have come back on the same sites involved before. Of course, of the 11 patients that Shoch and Alexander reported on, 1 had three reinfections in a period of a year. But in view of the fact that the lesions came in the same site as the original primary lesion, I agree with the diagnosis of recurrence or relapse. Rattner, of Chicago, has treated about 453 patients with intravenous drip, and in a recent communication he told me that he has been having less recurrences recently, since he has used injections of a bismuth preparation along with the intravenous drip.

DR. R. E. BARNEY: What is to be done next? The Wassermann reaction has remained positive throughout. I think that the possibility of reinfection can be ruled out. I believe that it is a recurrent syphilid. I do not know whether the lesions are multiple chancres or papuloerosive secondary lesions, but I favor the latter explanation. Regardless of type, is it wise to repeat intensive therapy? Or should use of mapharsen and bismuth three times a week be continued? It seems to be a virulent type of infection.

DR. H. N. COLE: I think that there would be no harm in giving intravenous drip again.

DR. R. E. BARNEY: Do you not think that his wife should be treated intensively?

DR. H. N. COLE: Yes.

DR. H. G. MISKJIAN: This may be an arsenic-resistant syphilis. I have seen several such cases in years past. I think that for this reason it would be better to change the treatment and not give arsenic again. I suggest a trial of some other form of therapy.

DR. H. N. COLE: There is another method which might be employed. Dr. Robert Stecher might use hypertherm therapy on the patient, and then along with this perhaps three syringe injections of arsenic could be given. Dr. Miskjian's remarks are apropos.

DR. R. E. BARNEY: Do you think that this is possibly an arsenic-resistant syphilis?

DR. H. N. COLE: I do not think that it is. However, I recommend the giving of injections of a bismuth preparation as well as the intravenous drip treatment.

Lichen Striatus. Presented by DR. E. W. NETHERTON.

E. B., a married woman aged 44, states that about five weeks ago she began to have periodic attacks of burning and itching on the upper posterior surface of the right thigh. About a week later a red spot developed, and within a day or so a bandlike eruption had appeared and extended from the right buttock downward over the posterior surface of the thigh, calf of the leg and forward to involve the whole lateral surface of the right foot. She was impressed by the rapidity of development of the eruption. Itching had remained but had not been intense.

There is a unilateral, linear, lichenoid, erythematosquamous eruption involving the right buttock, the posterior surface of the right thigh and leg and the lateral surface of the right foot. The lesions do not form an uninterrupted band or streak, but instead there are narrow, superficial, light red to yellowish pink, smooth and scaly bands, papules and small plaques in linear formation. The scales are large, thick and adherent. The papules are small and flat but are not angular or umbilicated. The mucosa and the other cutaneous surfaces are free of lesions. Wickham's striae are not present.

A punch biopsy performed on the lesion on the thigh showed the following changes: On the surface of the epidermis there was a loosely packed hyperkeratotic scale with a few small islands of parakeratosis. The granular layer was present but thin and interrupted. There was moderate irregular acanthosis. There was slight intercellular and pronounced intracellular edema in the rete mucosa. Wandering cells were present in the most edematous areas of the epidermis. The basal layer was intact. The papillary and subpapillary layers showed pronounced edema, dilatation of the blood vessels and loose perivascular lymphocytic infiltration. Nevus cells were not observed. The inflammatory changes did not extend below the subpapillary layer. A histologic diagnosis of lichen striatus was made.

DISCUSSION

DR. H. N. COLE: I think that this is a remarkable example of lichen striatus.

DR. E. W. NETHERTON: I might add a few words regarding the cases that were reported by Drs. Senear and Caro (ARCH. DERMAT. & SYPH. **43**:116 [Jan.] 1941). They reported 10 cases of lichen striatus, and in 7 of the cases the disease occurred in children of 3 to 15 years of age. The eruption occurred on the upper extremities or on the neck. They did not observe a case in which the lower extremities were involved. In 1 of their cases the lesions were bilateral, involving each side of the neck. The eruption disappeared spontaneously in a relatively short time.

Circumscribed Myxedema. Presented by DR. R. E. BARNEY.

A. K., a Negro aged 54, was presented before this society a year ago (ARCH. DERMAT. & SYPH. **47**:425 [March] 1943) with a diagnosis of circumscribed myxedema. Some of the members favored a diagnosis of elephantiasis. Since that time there has been a gradual progression of the eruption, and now the papillary hypertrophy of the skin of the legs, especially above the ankles, is more pronounced.

DISCUSSION

DR. R. E. BARNEY: I presented this patient last year with a diagnosis of circumscribed myxedema, but both Dr. Cole and Dr. Netherton thought the disease was a form of elephantiasis. The histologic changes in circumscribed myxedema show the myxomatous tissue occupying the entire corium. The biopsy specimen from this patient shows only a small zone in the corium just below the papillary layer which resembles myxomatous degeneration. In this specimen the epidermis is acanthotic and there is widespread fibrosis in the corium with dilatation of the lymphatics. I now think this is a case of elephantiasis nostras.

A Case for Diagnosis (Psoriasis, Aberrant Type?). Presented by DR. MAX E. KRAUSE and (by invitation) DR. H. N. COLE JR., and DR. ROBERT CORD.

E. D., a white boy aged 13, presented from the department of dermatology and syphilology, Cleveland City Hospital, states that he was well until one year ago, when a slightly pruritic eruption developed on the left thumb; it gradually spread to involve the entire palmar surface of the left hand. Approximately one month ago the eruption spread to the other palm, then gradually extended up the arms and over the trunk and simultaneously appeared on the lower extremities and genitalia.

There is a fairly symmetric erythematous, scaly eruption of the palms, arms, trunk and lower extremities. On the palms the skin is thick, red and shiny and covered with adherent grayish white scales. Complete extention of the fingers is impossible owing to the contraction and fissuring of the skin. This eruption extends up the flexor surfaces of the arms, gradually fading into only an erythematous finely scaling dermatitis. On the abdomen the eruption is demarcated. On the lower extremities it has a marmoraceous appearance. Two small scaling plaques are present on the left knee; otherwise the extensor surfaces are relatively free of involvement. The scalp presents an admixture of adherent yellowish gray scales and crusts.

The axillary lymph nodes are enlarged but not tender. Otherwise the physical condition is essentially normal. The hemogram and urinalysis were normal. Serologic tests of the blood for syphilis gave negative results. Chemical examination of the blood showed 146 mg. of cholesterol and 9.7 mg. of calcium per hundred cubic centimeters of whole blood. A roentgenogram of the chest revealed no abnormal mediastinal or pulmonary changes.

Histologic examination of a section of skin taken from a lesion on the right wrist revealed slight hyperkeratinization with several areas of mild parakeratosis of the epidermis. The granular layer was present throughout, although in places it was much reduced. In one section both granular and horny layers were absent. The epidermis was slightly thickened and edematous, and the cells were not well defined. Several areas show *altération cavitaire*. The basal layer had lost its character, and the cells were edematous. The papillary pegs and papillae were irregular and in several places elongated. The corium was practically normal save for a small amount of perivascular cellular

infiltration made up mostly of lymphocytes and a few polymorphonuclear cells.

DISCUSSION

DR. H. J. PARKHURST, Toledo, Ohio: I thought that there was some resemblance to psoriasis, but I feel that it is not psoriasis because there were no sharply outlined patches. This is probably a case of congenital ichthyosiform erythroderma. It has predilection for the flexor surfaces, with redness and dryness.

DR. H. A. HAYNES JR., Akron, Ohio: I think it would be of interest to examine scrapings and possibly make a culture on Sabouraud's medium. It made me think of a trichophyton infection. The hands have the somewhat glazed appearance. Some of the other lesions resemble moniliasis.

DR. H. N. COLE: Some of the lesions, on the hands particularly, make me think of pityriasis rubra pilaris, but I do not believe there is enough exaggeration of the openings of the hair follicle on the fingers and over the knees to justify that diagnosis. It is a rare and unusual eruption.

Dr. J. R. DRIVER: I had the impression that Dr. Parkhurst did, that it is congenital ichthyosiform erythroderma.

DR. H. G. MISKJIAN: I first saw this patient in my office. At that time he had a mild scaling on the palm of one hand, with no redness whatever. It was just like a contact dermatitis, of which one sees numerous examples these days, and I did not in the least imagine it would turn into an eruption of this type. The second time I saw him was at the City Hospital, only about six weeks after my first examination, and the eruption had already attained its present extent and intensity. It must, therefore, have developed in a short time. In examining the lesions on the hands and forearms I would not hesitate to call this psoriasis. I may be wrong, but I scraped the lesions carefully and found all the characteristic layers that I had been taught to look for in psoriasis during my student days. The next thing was to explain the diffuse erythematous eruption on the chest and determine its relationship to psoriasis. This is what makes this case so interesting. I cannot call the superficial, dry, scaly erythema on the chest and trunk a form of psoriasis. Will it eventually develop into a psoriasis or is it some other disease? At present I cannot tell.

PHILADELPHIA DERMATOLOGICAL SOCIETY

CARROLL S. WRIGHT, M.D., *Chairman*

CARMEN C. THOMAS, M.D., *Secretary*

Nov. 19, 1943

Symposium on ocular syphilis, presented by the staff of the clinic for treatment of ocular syphilis of the Wills Hospital: Dr. Joseph V. Klauder, Dr. Marjory K. Hardy, Dr. John F. Wilson and Dr. George P. Meyer.

The Psychic Reaction of the Patient to Blindness —a Blind Man with a "Seeing Eye" Dog.

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It is unfortunate that treatment of atrophy of the optic nerve in the Negro becomes more difficult from the fact that he is usually immune to the tertian strain of malaria. Fever therapy by means of mechanical diathermy or by inoculation with a quartan strain of malaria is not easily available. This is a public health problem in which the department of health of every large municipality should be concerned.

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infiltration made up mostly of lymphocytes and a few polymorphonuclear cells.

DISCUSSION

DR. H. J. PARKHURST, Toledo, Ohio: I thought that there was some resemblance to psoriasis, but I feel that it is not psoriasis because there were no sharply outlined patches. This is probably a case of congenital ichthyosiform erythroderma. It has predilection for the flexor surfaces, with redness and dryness.

DR. H. A. HAYNES JR., Akron, Ohio: I think it would be of interest to examine scrapings and possibly make a culture on Sabouraud's medium. It made me think of a trichophyton infection. The hands have the somewhat glazed appearance. Some of the other lesions resemble moniliasis.

DR. H. N. COLE: Some of the lesions, on the hands particularly, make me think of pityriasis rubra pilaris, but I do not believe there is enough exaggeration of the openings of the hair follicle on the fingers and over the knees to justify that diagnosis. It is a rare and unusual eruption.

Dr. J. R. DRIVER: I had the impression that Dr. Parkhurst did, that it is congenital ichthyosiform erythroderma.

DR. H. G. MISKJIAN: I first saw this patient in my office. At that time he had a mild scaling on the palm of one hand, with no redness whatever. It was just like a contact dermatitis, of which one sees numerous examples these days, and I did not in the least imagine it would turn into an eruption of this type. The second time I saw him was at the City Hospital, only about six weeks after my first examination, and the eruption had already attained its present extent and intensity. It must, therefore, have developed in a short time. In examining the lesions on the hands and forearms I would not hesitate to call this psoriasis. I may be wrong, but I scraped the lesions carefully and found all the characteristic layers that I had been taught to look for in psoriasis during my student days. The next thing was to explain the diffuse erythematous eruption on the chest and determine its relationship to psoriasis. This is what makes this case so interesting. I cannot call the superficial, dry, scaly erythema on the chest and trunk a form of psoriasis. Will it eventually develop into a psoriasis or is it some other disease? At present I cannot tell.

PHILADELPHIA DERMATOLOGICAL SOCIETY

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admission both optic nerves were pale. Visual acuity corrected in the right eye was 3/60 and in the left 6/12. Perimetric fields were full; there was a central scotoma in the right eye. The patient was inoculated with malaria in May 1942 and had 12 fever paroxysms ranging from 103 F. to 106 F. Following convalescence from malaria he received, from June 1942 to December 1942, fourteen injections of neoarsphenamine (0.6 Gm. at each injection), eight injections of bismuth subsalicylate in oil (2.5 cc. each injection), and nine Swift-Ellis subdural treatments. He left the city in December 1942 and while absent had jaundice and fever and lost weight. On his return to the clinic in April 1943 arsenical treatment was withheld. Bismuth and subdural therapy were continued. The serum of another patient receiving arsenical therapy was employed for subdural injection. Visual acuity now is 3/60 in the right eye and 6/15 in the left eye. Perimetric fields are full. The central scotoma in the right eye is unchanged. The serologic reactions of the blood and spinal fluid are now negative; they were positive on his admission to the hospital.

DISCUSSION

DR. J. V. KLAUDER: From studies conducted by Moore and his collaborators (Moore, J. E.; Hahn, R. D., and Woods, A. C.: The Treatment of Syphilitic Optic Atrophy, *Am. J. Syph., Gon. & Ven. Dis.* **26:** 407-473, 1942), it was concluded that subdural treatment by the Swift-Ellis technic should be abandoned. I do not think that a critical study of our case records of optic atrophy would support that statement. After all, if one removes that method of treatment from the therapeusis of optic atrophy, there is little left, since a large percentage of the patients are not physically qualified for any form of fever therapy.

DR. GEORGE P. MEYER (by invitation): I made an analysis of some 40 cases a year or so ago for an ophthalmologic group and did not find pallor as the only symptom in any of the cases. In other words, I believe that the gross change indicated by the presence of pallor should be preceded by functional changes. Pallor is a late gross result rather than an early diagnostic sign. If one were to depend on pallor as the guide post for the institution of treatment, it would be too late in the vast majority of cases. If the fields in these cases are studied carefully, not only as to form but as to color, I believe with few exceptions one would find that changes in the fields antedate pallor. In all textbooks one reads of exceptions to that rule, but I think that this is the current ophthalmologic opinion.

DR. CARMEN C. THOMAS: If form fields are normal, would you consider pallor alone a contraindication to the administration of tryparsamide?

DR. GEORGE P. MEYER (by invitation): I should want to confirm the normality of the fields. If the patient had normal vision and I thought the disks were pale, I would be so confused that I would have to resolve that confusion by making quantitative perimetric color studies. If I found that all functional tests gave normal results I do not think there would be any contraindication to the use of tryparsamide, because the only explanation of the pallor would be an anomalous color, probably normal for that person. It is known that disks vary in their redness; some look positively inflamed and yet may be normal. There is a wide variability in the normal range on the pink side. Of course the presence of pallor would make me proceed with tryparsamide with much trepidation. I would check up on the fields regularly and question the patient for any subjective symptoms he might have. I consider damage to the optic nerve most certainly a contraindication to the use of tryparsamide.

DR. NORMAN R. INGRAHAM: Why is that a contraindication?

DR. GEORGE P. MEYER (by invitation): I have never had that question asked before. I think the reason is that damaged tissues are more susceptible to injury. If one uses tryparsamide and damage to the nerve results, the nerve may recover; but if one barges ahead and gives more, blindness is certainly going to result. Occasionally, in giving antisyphilitic treatment there is an increase in symptoms—what might be called a Herxheimer reaction—but that does not interfere with the continuation of treatment. I think experience bears out that continuing the treatment in such cases does not do damage. But if one continues the use of tryparsamide in the presence of a damaged nerve, one will get blindness.

DR. SIMON KATZ: How much contraction?

DR. GEORGE P. MEYER (by invitation): Any contraction that leaves no doubt that damage has been done would contraindicate tryparsamide. If I discovered a 5 per cent contraction in the field, I should not use tryparsamide.

DR. THOMAS BUTTERWORTH (Reading): How do you treat the toxic amblyopia of tryparsamide here? In another city I saw a man who had that, and he was given enormous doses of vitamins A and B.

DR. J. V. KLAUDER: That is in accordance with the studies of McDermott and his collaborators (Webster, B.; Baker, R.; Lockhart, J.; Tompsell, R., and McDermott, W.: Nutritional Degeneration of the Optic Nerve in Rats: Its Relation to Tryparsamide Amblyopia, *J. Pharmacol. & Exper. Therap.* **77:**24-39, 1943), who prevented atrophy of the optic nerve in rats treated experimentally with pentavalent arsenic by giving these vitamins. I venture a guess that if one were to examine 100 persons who had had tryparsamide at any period of their syphilitic treatment an appreciable percentage would show a contraction of their fields, even though the treatment had been given years before without subjective symptoms. When a patient is first seen, it may be difficult to decide whether or not atrophy of the optic nerve was caused by prior administration of tryparsamide or by the neurosyphilitic process.

DR. ISADORE ZUGERMAN: How would the danger of tryparsamide compare with that of any other pentavalent arsenic preparation?

DR. J. V. KLAUDER: I think that what has been said applies to any pentavalent arsenic preparation.

DR. JOHN W. LENTZ: Dr. Beerman and I have a short series of cases in which we gave aldarsone (sodium methylenesulfonaminohydroxyphenylarsenate) to persons with contracted fields from tryparsamide, and 2 of them have received forty injections without any trouble at all, so far as we can tell.

DR. J. V. KLAUDER: With no effect on the atrophy of the optic nerve?

DR. JOHN W. LENTZ: None, so far as the ophthalmologist can tell. We do not know what the result will be as far as the syphilis is concerned.

Stationary (?) Atrophy of the Optic Nerve of Fourteen Years' Duration.

N. M., a white man aged 52, was first seen in 1926. He was treated in the ophthalmologic clinic for retinitis. Visual acuity in the right eye was 6/10 and in the left eye 6/10. The optic disks were paler than normal. No

record of perimetric fields in 1929 can be found. He had neurologic signs of tabes, and serologic reactions of the blood and spinal fluid were positive. From 1929 to 1932 he received thirty injections of an arsenical and sixty-eight injections of a bismuth compound. He lapsed treatment from 1932 to 1939. In 1939 he complained of failing vision of seven months' duration. Both optic disks were pale. The perimetric fields were contracted to approximately 30 to 60 degrees in the right eye and from 30 to 50 degrees in the left eye. Visual acuity in the right eye was 6/15 and in the left eye 6/21. He received malarial therapy and had six fever treatments. From 1939 to date he has received fifty-eight injections of a bismuth compound, twenty-eight arsenical injections and six Swift-Ellis treatments. His optic disks are still pale. The perimetric fields are about the same as in 1939. Visual acuity in the right eye is 6/21, with correction 6/6—2, and in the left eye 6/30, with correction 6/21.

DISCUSSION

DR. J. V. KLAUDER: I think that ophthalmologists should become more conscious of syphilis and syphilologists more conscious of the ocular lesions of the disease. Either syphilologists should examine eyegrounds and the personnel of syphilis clinics be trained to conduct perimetric studies or an ophthalmologist should be included in the staff of such clinics. Referring patients to another clinic (opthalmologic) for such examination is usually not satisfactory.

Postneuritic Atrophy of the Optic Nerve in Congenital Syphilis.

M. D., a Negro girl aged 14, was first seen in March 1943. She had sudden onset of impaired vision of the right eye in January 1943, and three weeks later of the left eye. At the onset she had headaches. The Wassermann reaction of the blood was strongly positive. The optic disks were pale, which was regarded as secondary to optic neuritis. The visual acuity of the right eye was 2/60 and of the left 3/60. There was weakness of the right and left external rectus muscles. The pupils were equal and regular and reacted to light. The biceps, triceps, patellar and Achilles reflexes were normal. A roentgenogram of the skull and sinuses revealed no changes. Examination of the spinal fluid gave normal results in all phases.

Juvenile Tabes with Rapidly Progressing Atrophy of the Optic Nerve.

M. H., a Negro girl aged 16, was first seen on June 28, 1943. Two weeks previously she had struck her head on the door of an oven. The injury was apparently trivial. From that time vision rapidly diminished. At the end of a week she could see only hand movements. There are no stigmas of congenital syphilis. The pupils are dilated and do not react to light. The patellar and ankle reflexes are absent. The Wassermann reaction of the blood is strongly positive. The reaction of the spinal fluid is positive in all phases. The optic nerves are white. Visual acuity in both eyes is limited to hand movements only.

DISCUSSION

DR. J. V. KLAUDER: We are seeing too many juvenile patients with tabes and atrophy of the optic nerve. Our oldest patient was aged 28 when he first noticed impaired vision. Years will elapse after successful operation of laws requiring premarital serologic tests before the atrophy of the optic nerve caused by congenital syphilis is abolished.

Optic Neuritis Appearing During Antisyphilitic Therapy.

M. H., a white man aged 20, was first seen in April 1943. He had impaired vision of both eyes of three weeks' duration. He had no knowledge of a syphilitic infection. The Wassermann reaction of the blood was found positive on routine examination for military service. He received ten injections of a bismuth compound and thirteen injections of mapharsen. This treatment was continuous up to the time of impaired vision. On admission, visual acuity of the right eye was counting fingers at 2 feet (60 cm.); of the left eye, 1/60. There was pronounced congestion of both disks with obscuration of details. There was no swelling or exudate. Other than impaired vision, there were no subjective symptoms. The Wassermann reaction of the blood was strongly positive. The reaction of the spinal fluid was negative in all phases. Arsenical and bismuth therapy was continued, potassium iodide also being administered. The congestion of the disks gradually disappeared. Both disks now show temporal pallor. The perimetric fields are full. Visual acuity is 6/21 in each eye.

DISCUSSION

DR. J. V. KLAUDER: This is an interesting case. It is to be noted that the optic neuritis was not a symptom of a neurorecurrence. Is its pathogenesis comparable to the ninth day erythema of Milian? Is it an expression of neurosyphilis despite the fact that the spinal fluid gives a negative reaction for syphilis? I am not willing to attribute optic neuritis to syphilis unless it is associated with symptoms of neurosyphilis, especially of the acute meningeal type, appearing in early syphilis and accompanied by a positive spinal fluid. Other writers are not of this opinion. For example, Woods (Syphilis of the Eye, *Am. J. Syph., Gonor. & Ven. Dis.* **27**:133-186, 1943) has stated that optic or retrobulbar neuritis may be present without clinical or serologic evidence of acute meningeal syphilis. In such an event, how can one be certain that the process is caused by syphilis? It appears to me that this implies a localized form of neurosyphilis. I do not believe that such form is seen in the clinical domain of neurosyphilis.

Interstitial Keratitis — Recurrence in the First Eye Without Involvement of the Second Eye.

C. S., a white man aged 37, was first seen in December 1938, with active interstitial keratitis affecting the left eye. At that time alternating courses of neoarsphenamine and bismuth subsalicylate were given, until a total of thirty injections of the arsenical and sixty injections of bismuth was administered. This formula of treatment was completed in April 1941, at which time visual acuity in the left eye was 6/15 + 2 and in the right eye 6/9 + 2. In September 1943 the left eye became irritable and the cornea hazy. The clinical diagnosis of interstitial keratitis was confirmed by slit lamp examination. The right eye has never become involved. The Wassermann reaction of the blood at the time the patient was first seen was negative, and it has remained negative. The patient's mother has a positive Wassermann reaction and is receiving treatment in another hospital.

DISCUSSION

DR. J. V. KLAUDER: Recurrence of interstitial keratitis after supposedly adequate treatment raises the

question: Was the treatment adequate or is interstitial keratitis solely a syphilitic disease? This recalls an occasion when I made ward rounds with Nonne at the Eppendorf Hospital, in Hamburg. After he had shown me a patient, I remarked, "That would not have happened if he had had adequate treatment"; and Nonne replied, "What is adequate treatment?" That applies, I think, to the whole question of the treatment of syphilis and perhaps to the therapeusis of any disease; what is adequate for one is not adequate for another. For this patient I predict that the second eye will eventually become affected. The longer one observes these patients the greater is the incidence of involvement of the second eye.

DR. FRED D. WEIDMAN: Was he proved to be syphilitic?

DR. J. V. KLAUDER: His mother is syphilitic. She is receiving treatment at another hospital. He has the facies of congenital syphilis. The negative Wassermann reaction correlates with his age. The older the patient, the greater the incidence of negative serologic reactions of the blood; the younger the patient and the more active the disease, the greater the likelihood of positive reactions. The nearest approach to 100 per cent is an acute attack in a child. (Klauder, J. V., and Vandoren, E.: Interstitial Keratitis — Standardization of Treatment, *Ven. Dis. Inform.* **22**:307-322, 1941.)

DR. FRED D. WEIDMAN: What are the statistics as to the causes of interstitial keratitis other than syphilis?

DR. GEORGE P. MEYER (by invitation): Frankly, I do not believe that in all cases an accurate differential diagnosis can be made. There are other causes for interstitial keratitis, the chief of which is tuberculosis; and there are some ophthalmologists, like Dr. Cowen, who feel sure that they can make a positive diagnosis of syphilitic keratitis in contradistinction to tuberculous keratitis. Most of us recognize the common manifestations of syphilitic interstitial keratitis and can make the diagnosis, but I do not believe that a hard and fast differential diagnosis can always be made. I believe with Dr. Klauder that in the vast majority of cases interstitial keratitis is of syphilitic origin. I am speaking of diagnoses both by gross examination and by slit lamp.

DR. NORMAN R. INGRAHAM: How would you go about making a differential diagnosis? Would you use the slit lamp, or what other means of differential diagnosis would you use?

DR. GEORGE P. MEYER (by invitation): Dr. Klauder was speaking of gross examination with direct illumination in contradistinction to illumination with the slit lamp. Other than that there are no methods of diagnosis. If a patient is tuberculous, with a positive Mantoux reaction, the interstitial keratitis may be regarded as tuberculous; one may say that the person is tuberculous or syphilitic, but the presence of either disease does not prove that it is the cause of the interstitial keratitis. My chief, Dr. Adler, and I were interested in the question of differential diagnosis, and, granted that practically 100 per cent of the urban population have a tuberculin sensitivity, of what value is a Mantoux test? We felt that if we did a Mantoux test and the lesions were tuberculous, we could demonstrate a higher degree of sensitivity than in the average person. This in our experience proved to be clinically true.

DR. NORMAN R. INGRAHAM: Is it advisable to treat a syphilitic interstitial keratitis?

DR. J. V. KLAUDER: The nonsyphilitic type of interstitial keratitis responds to fever therapy. I think Dr. Ingraham in his first question was referring more to the gross appearance—the mutton fat deposits which are supposed to be distinctive of tuberculous keratitis.

DR. GEORGE P. MEYER (by invitation): Mutton fat deposits are deposits of uveal exudate that form on the surface of the cornea. They are not characteristic of keratitis. That is a part of the picture that is apart from keratitis. In true keratitis one need not have these deposits. In tuberculous disease the deposits are most apt to take the mutton fat form, but that does not establish the diagnosis of keraitis. It establishes uveal disease.

DR. J. V. KLAUDER: Perhaps Dr. Ingraham had in mind the location of the deeper vessels in interstitial keratitis.

DR. GEORGE P. MEYER (by invitation): When typical brushlike vessels are observed, that is practically diagnostic of syphilitic infection; but that is talking of things past and gone. But in the early stage, when photophobia prevents a good slit lamp examination, it is difficult. Slit lamp examination performed by an expert, together with the characteristic clinical findings, offers the best chance of an accurate diagnosis.

Chorioretinitis of Congenital Syphilis.

D. E., a white woman aged 24, first visited the clinic in 1930, complaining of poor vision since 2 years of age. She had stigmas of congenital syphilis. The Wassermann reaction of the blood was strongly positive. The Wassermann reaction of her mother was strongly positive, but those of an older brother and a younger sister were negative. Examination of the fundus of the right eye revealed that the media were clear. The disk was somewhat pale and covered with connective tissue. There was pronounced vascular sheathing about the vessels leaving the disk. There was diffuse pigmentary disturbance particularly in the periphery, giving the appearance of the salt and pepper fundus. Pigmentary changes were present around the macula. In the left eye the media were clear. There were diffusely scattered deposits of pigment throughout the fundus which did not follow a vascular distribution. These deposits were not of the lacy type seen in retinitis pigmentosa. Pigmentary disturbance in the region of the macula could account for loss of vision. There were no isolated chorioretinal atrophic areas surrounded by pigment. Visual acuity of the right eye was 6/60, with correction, 6/6; of the left eye, 6/60, with correction, 6/30. Arsenical and bismuth therapy was given at intervals for two years. The appearance of the fundi and the visual acuity have remained unchanged. The Wassermann reaction of the blood is negative.

DISCUSSION

DR. J. V. KLAUDER: About 10 per cent of persons with congenital syphilis have peripheral chorioretinitis which persists throughout life. Routine fundus examination may therefore be of diagnostic help in the clinical study of a patient the Wassermann reaction of whose blood is positive. Choroiditis does not often involve the region of the macule or cause secondary atrophy of the optic nerve. I do not regard it as an important cause of blindness, but I give it fourth or fifth place in my impression of the ocular lesions of syphilis that cause blindness.

Syphilitic Iritis — Incidence; Fever Therapy; Herxheimer Reaction as a Diagnostic Aid.

Incidence.—The following data were compiled by Dr. M. K. Hardy from case records of patients who had

active lesions of syphilis in various stages of the infection. These patients were studied either by her or Dr. Klauder.

Primary Syphilis: Of 79 patients (all males) who had a chancre observed in the presecondary stage of syphilis, none had iritis.

Secondary and Late Secondary Syphilis: Of 111 patients, 40 per cent of whom were Negroes, 4 had iritis (3.6 per cent).

Late Syphilis: Of 86 patients with lesions of late syphilis affecting the skin, mouth, throat or bone, none had iritis.

Of 18 patients with iritis regarded as caused by syphilis, there were 12 males and 6 females; 14 were Negroes. The youngest was 18 years of age; the oldest, 61. Iritis was observed in these patients in the late secondary stage, usually when retrogressing lesions of the secondary eruption were still present. There were 2 exceptions. One patient had leukoderma; the other had condylomas. In 7 (all Negroes) the eruption was of the papular type. Of the 18 patients, the iritis was unilateral in 72.2 per cent and bilateral in 27.8 per cent.

Fever Therapy.—G. M. S., a Negress aged 23, when first seen, in March 1943, had an acute iritis of the right eye of one month's duration. She also had mucous patches, leukoderma of the neck, pigmentary remains of a former eruption and condylomas. The Wassermann reaction of the blood was strongly positive. She had received no treatment prior to coming to the clinic.

Initial treatment consisted of fever therapy only—four intravenous injections of pyrifer (a colon bacillus vaccine for producing artificial pyrexia) administered every other day. The peak temperatures resulting from these injections were 104 and 103 F. Following this treatment, bismuth and arsenical therapy was instituted. There was an appreciable improvement of the iritis twenty-four hours after the first injection of pyrifer and striking improvement after completion of fever therapy. Ten days later on gross examination there was no evidence of inflammation in the affected eye. Slit lamp examination on the twelfth day showed that the cornea was fairly clear, the aqueous fluid clear and no turbidity and no cells present. This was in contrast with the conditions observed on slit lamp examination before fever therapy. It was our impression that the iritis retrogressed more quickly than in patients treated only with bismuth and arsenic.

Herxheimer Reaction.—W. C., a white man aged 63, was first seen on Sept. 15, 1941, with bilateral plastic iritis. The onset occurred in the right eye two months previously. Visual acuity of the right eye was 6/15—2, with correction 6/12 + 2; of the left eye, 6/30, with correction also 6/30. He presented a macular syphilid in the retrogressing stage with some pigmentary remains of former lesions; there was no evidence of a chancre. The Wassermann reaction of the blood was strongly positive in all dilutions. The patient had previously been untreated.

To determine whether or not aggravation of inflammatory symptoms occurred after injection of neoarsphenamine, a large dose (0.6 Gm.) was purposely administered. Slit lamp examination made before and eighteen hours after injection was reported as follows:

"Slit Lamp Examination Before Injection (Sept. 16, 1941, 4 p. m.).—Right Eye: There is generalized faint haziness of the cornea, with a few wrinkles in Descemet's membrane. There are a large number of old and some still active corneal precipitates on the posterior surface of the cornea. The aqueous is slightly turbid and contains several cells. The iris is somewhat dull. There are pigment granules on anterior capsule of lens. The lens is clear, and there are no nodules on the iris.

"Left Eye: The cornea is moderately hazy, with a synechia at 6 o'clock. The aqueous is turbid, with numerous active corneal precipitates on the posterior surface of the cornea. The iris is dull and edematous. There is considerable pigment on the anterior capsule of the lens. The lens itself appears clear. There are no nodules on the iris.

"Slit Lamp Examination Eighteen Hours After Injection.—There is an increased haziness of the cornea. The corneal precipitates are more pronounced, and there are more cells in the aqueous."

Examination twenty-seven hours later showed that the aqueous of the right eye was slightly clearer, with only an occasional cell; the left eye was unchanged. Two weeks later slit lamp examination revealed that both eyes were decidedly improved. Six weeks later, examination revealed no inflammatory activity and the cornea and aqueous fluid of both eyes were clear. There was an old posterior synechia in the left eye. Prior to this examination the patient had received six injections of 0.6 Gm. neoarsphenamine administered at weekly intervals. A soluble bismuth compound was given conjointly with the first two injections of the arsenical.

Now the visual acuity is: right eye, 6/21, with correction, 6/6; left eye, 6/21, with correction, 6/6. The patient has about completed the quota of treatment for early syphilis. Serologic tests of the blood and spinal fluid elicited negative reactions.

Iridorecurrence Resulting in Loss of Vision.

J. W., a white man aged 25, had a genital lesion in September 1939, which persisted for three weeks. He received five intravenous injections at weekly intervals and then lapsed treatment, the last injection being in early October. He first visited this clinic on Nov. 20, 1939. The left eye had become inflamed two weeks previously and the right eye approximately ten days later. He presented bilateral iritis, which was more severe in the left eye. There was a nodule in the right iris. The Wassermann reaction of the blood was strongly positive. There was no evidence of secondary syphilis. Visual acuity of the right eye was 5/60; of the left eye, counting fingers at 6 feet (183 cm.). The patient was hospitalized for one month. Treatment consisted of weekly injections of 0.4 Gm. of neoarsphenamine. A soluble bismuth compound was given conjointly with the arsenical for five consecutive injections. After receiving eight injections of neoarsphenamine, he lapsed treatment in January 1940. At that time the iritis of the right eye had retrogressed. The left eye showed disorganization of the iris with considerable atrophy of the stroma; there was a membrane extending from the iris to the anterior capsule of the lens, and there were deposits on the posterior surface of the lens with loss of vitreous architecture. The patient returned to the clinic in October 1940, with recurrence of inflammation in the left eye—acute anterior uveitis. He has since attended regularly and has received the quota for early syphilis. Serologic tests of the blood and spinal fluid for syphilis elicited negative reactions. The left eye is now enlarged, with increased finger tension. The iris is atrophied, with numerous posterior synechiae. The anterior capsule is thickened and opaque. The diagnosis is secondary glaucoma. The visual acuity is nil. The visual acuity of the right eye is 6/9 + 4.

DISCUSSION

DR. J. V. KLAUDER: I think the best criterion that iritis is caused by syphilis is its appearance in the early stage of the disease or in the time period during which late secondary mucocutaneous lesions may appear. I am skeptical of syphilis as the cause of iritis appearing in the late stage of infection. Some ophthalmologists believe that the presence of a positive Wassermann reaction suffices to warrant the diagnosis of syphilitic iritis. Is not that comparable to diagnosing an eruption as syphilitic or a pain in the stomach as of syphilitic causation if the patient has a positive Wassermann reaction of the blood? It is interesting to note that Guyton and Woods (Etiology of Uveitis, *Arch. Ophth.* **26**:983-1013 [Dec.] 1941) have expressed themselves as regarding uveitis appearing in late syphilis as of syphilitic causation if there is a favorable response to antisyphilitic treatment. One may ask what is the criterion of a favorable response? Evaluation of the therapeutic test is difficult in ocular lesions. One sees considerable improvement after dilation of the pupil in the absence of any treatment. Moreover, there is apparently a nonspecific effect of antisyphilitic compounds on inflammatory ocular lesions. Mercury has long been used for this effect. In order to establish a criterion, we are determining whether the Herxheimer reaction is of diagnostic significance and also the amount of antisyphilitic treatment that is required to result in disappearance of all inflammatory symptoms, as studied by slit lamp examination, in patients with iritis associated with lesions of late secondary symptoms.

Perhaps a pathologic visualization by Dr. Weidman would be helpful. What are the chances of an ulcerative or destructive type of ocular lesion in late syphilis as opposed to an acute exudative type of lesion—for example, the acute inflammation of iritis in early syphilis versus a gumma of the iris or ciliary body in late syphilis?

DR. FRED D. WEIDMAN: You are appealing to me as a general pathologist, and the answer is that a general pathologist just does not see such lesions. A pathologist is supposed to be most useful from information he gains at the necropsy table. It is my personal experience that such patients simply do not appear at the necropsy table or if they do, perchance, not often enough for anybody to form an opinion. Accordingly, I can come to an opinion only on the basis of general principles in pathology. Now, in the final analysis, what one regards as an acute iritis clinically will be regarded as such largely on the basis of congestion and exudation. For the eye, these phenomena could occur in the "chronic" as well as in the "acute" stage of syphilis. That is, the lesion is acute in terms of pathologic processes and to all intents and purposes is occurring in what is regarded as the chronic stage of the disease—chronic in point of time. The general pathologist insists on distinguishing between "point of time" and "pathologic processes" when he is discussing "acute" and "chronic." Now, that is the situation, I should say, in which a lesion of late syphilis as seen in a place like the eye, where it can be checked by direct inspection, would exhibit the reactive phenomena which ordinarily would be regarded as acute; the relatively minor congestion concerned in a gumma could, in a place like the loose tissue of the iris, result in exudation. Accordingly, I should say that in spite of the fact that syphilitic iritis can occur in the fourth month or the eighth or eighteenth year of syphilis, the gross morbid expressions could be viewed as what one commonly regards clinically as an acute inflammatory reaction.

Gumma of the Orbit.

M. W., a Negro woman aged 52, complained of a nonpainful swelling of the right eye of three weeks' duration. She presented an obvious protrusion of the right eye, apparently caused by a retrobulbar mass. There were no signs of inflammation, no tenderness and no pain. The right upper lid was ptosed. The left eye was normal. The exophthalmometer reading of the right eye was 27; that of the left eye, 19. She had pupillary abnormalities and other neurologic signs of neurosyphilis. The temporal side of each optic disk was pale. Visual acuity of the right eye was 6/9; of the left eye 6/21. The perimetric field of the right eye was full; the field of the left eye revealed constriction on the temporal side to about 40 degrees. The Wassermann reaction of the blood was strongly positive, and the spinal

Gumma of orbit.

fluid was positive in all phases. A roentgenogram of the skull revealed no abnormality. Treatment was initiated with injections of a soluble bismuth compound and oral administration of potassium iodide. Later 0.2 Gm. of neoarsphenamine was given. This dose was gradually increased. There was a prompt improvement after treatment. The exophthalmos and ptosis gradually disappeared. In August the swelling was gone and the lid was no longer ptosed. The exophthalmometer reading was 20 in both eyes.

DISCUSSION

DR. GEORGE P. MEYER (by invitation): The diagnosis of gumma is a presumptive one. I think it deserves presentation and emphasis in view of the rarity of the condition. I should like to know whether anyone else has seen anything like it.

DR. J. V. KLAUDER: It is the first example we have seen of gumma of the orbit since this clinic was started fourteen years ago. We have seen many instances of swelling, for which we administered the therapeutic dose without success, but this is the first case in which it disappeared after treatment. I think that is a good indication that it was syphilitic. The patient has neurosyphilis. I think a therapeutic test is the only means of making a diagnosis.

DR. ISADORE ZUGERMAN: It is interesting that in this patient blindness did not develop because of pressure. Recently I had a case of cavernous sinus thrombosis with exophthalmos, and the patient became blind.

DR. J. V. KLAUDER: Apparently there was no pressure. There was no evidence of choked disk. It did not appear to exert pressure on the optic nerve.

Xanthomatosis, Juvenile. Presented by DR. J. M. SCHILDKRAUT (Trenton, N. J.).

J. M., a white boy aged 10 months, presents numerous pea-sized to quarter-sized reddish yellow elevations. Some of the lesions are rounded, but most are flat, round or oval elevations. They are present on the

forehead, nose, neck and head, behind the left ear, on the chest and in a grouped arrangement on the lower part of the abdomen and right thigh. Several are present on the back and buttocks. The tumors have grown with the growth of the child but have become flattened. The disease began when the child was about 4 months of age with the development of small yellowish growths scattered on the face, chest, lower part of the abdomen, buttocks and limbs. The child's father has been treated for syphilis. The physical examination of the patient shows nothing abnormal, and his general appearance is excellent.

The cholesterol content of the blood was 375 mg. Results of a urinalysis were normal. A roentgenogram of the skull did not show rarefaction. The patient has been put on a fat-free diet, with practically no change.

DISCUSSION

DR. FRED D. WEIDMAN: I think we were all struck by the yellowness of these lesions; the fat content must be exceedingly high in them. I was also struck by the fatness of the baby, and of course all of us realize the difficulty in treating such patients in that we must inquire into the subtler internal medical connections. I should say that the first avenue of approach would be the endocrine glands, investigating them from any angle whatever. The thyroid in particular would be the first to be considered in the attempt to find whether some one of these glands might be hit on which was upsetting the general balance between the various endocrine glands. I should say that the studies in relation to the thyroid and after that random experiments in therapy, perhaps of the adrenal glands and the gonads, would be the line to follow. I do not think this is an instance of the nevoxanthoendothelioma of McDonough; in the cases he recorded the lesions were on the face more particularly. The xanthomatous lesions in Hand-Schüller-Christian disease occur on the face particularly.

DR. J. M. SCHILDKRAUT (Trenton, N. J.): The child has been on a nonfat diet and seems to be thriving just on skim milk. He is gaining. He is not receiving any animal food. Physically he seems to be in good condition; there are no cardiac symptoms and no enlargement of the liver or spleen. How would Dr. Weidman go about studying the endocrine glands?

DR. FRED D. WEIDMAN: I should study hepatic function in particular; the adrenal glands and the liver are, of course, the main organs of cholesterol metabolism. The adrenals are more difficult to study clinically. I should perhaps investigate the blood pressure, but particularly I should study the hepatic function and the thyroid glands.

Xanthoma Tuberosum Multiplex. Presented by DR. MORRIS MARKOWITZ.

M. L., a Negro man aged 35, presented numerous shot to pea-sized yellow nodules, firm and elastic, on the elbows, thighs, knees and buttocks. On the palms the normal furrows are chamois-colored, somewhat elevated bands. The patient was treated for syphilis from 1936 to 1940. The present condition began approximately ten months ago on the elbows and spread to the other regions of the body.

A blood count on Sept. 19, 1943 revealed 76 per cent hemoglobin (10.5 Gm.); 3,740,000 erythrocytes; color index 1.0, and 7,250 leukocytes, with 4 per cent stab forms, 68 per cent segmented forms, 24 per cent lymphocytes, 3 per cent eosinophils and 1 per cent basophils. A determination of the blood chemistry on the same day showed: sugar, 74 mg. per hundred cubic centimeters; urea nitrogen, 14.3 mg., and creatinine, 1 mg. The cholesterol content of the blood plasma was 375 mg. per hundred cubic centimeters and of the whole blood, 300 mg.; the cholesterol ester content of the whole blood was 195 mg. The Wassermann reaction of the blood on September 22 was negative.

The report of the biopsy was as follows: The epidermis appeared normal. The corium showed an irregular nodule composed of proliferating fibrous connective tissue in which there were interspersed small, irregular clumps and strands of large foam cells which had an abundant finely granular eosinophilic cytoplasm and eccentrically placed large ovoid nuclei. Indistinct multinucleated giant cells (Touton cells?) were present.

DISCUSSION

DR. THOMAS BUTTERWORTH (Reading): I think that in this case the perifollicular deposition of the fat is shown beautifully. I suggest that Dr. Markowitz try a high carbohydrate diet with insulin for his patient. I can record definite disappearance of the lesions of 1 of my patients after about a year and a half of such treatment.

DR. J. M. SCHILDKRAUT (Trenton, N. J.): The strange thing about these patients shown tonight is that the man is syphilitic and the child has a syphilitic father. This may be merely a coincidence, of course.

CARROLL S. WRIGHT, M.D., *Chairman*

CARMEN C. THOMAS, M.D., *Secretary*

Jan. 21, 1944

Treatment of Cavernous Angioma. Presented by DR. SIGMUND S. GREENBAUM.

The lesion was on the cheek and chin. Twenty-three injections of quinine hydrochloride and ethyl carbamate were administered between March 21, 1942 and Dec. 31, 1943. Roentgen rays and radium were employed before this without beneficial results.

In a second patient there was a cavernous angioma of the entire right cheek, right lower eyelid and right side of the upper lip. It was treated with twenty-four exposures to radium filtered and unfiltered, and nineteen injections of quinine hydrochloride and ethyl carbamate between July 7, 1941 and Dec. 24, 1943.

DISCUSSION

DR. EDWARD F. CORSON: How was the radium used —large doses, plaques or needles?

DR. SIGMUND S. GREENBAUM: In 1 of these cases both the radium and the roentgen rays were applied by another physician. In the case of the extensive angioma I used surface radiation filtered through brass, and the red surface areas disappeared more or less completely, as you see. I might say that in discussing these cases with one of the dermatologists not here tonight, I was told that he had seen 1 sudden death from the injection of these sclerosing solutions. I do not know whether any one else has heard of such cases.

DR. CHARLOTTE BACKUS-JORDAN, Stroudsburg: I have—twenty-four to thirty-six hours afterward, but after injection for varicose veins.

DR. SIGMUND S. GREENBAUM: In my case the injection was for angioma, and death occurred imme-

diately on the table. I cannot see how sudden death can occur from such a procedure. We know that it occurs in cases of varicose veins, but in cases of cavernous angioma, in which the pathologic picture is so different, it is difficult to understand how death occurs.

DR. THOMAS BUTTERWORTH, Reading: How do you control the pain? I have tried using half-strength solution in a few cases, but invariably the baby cries so much that the mother does not bring it back.

DR. SIGMUND S. GREENBAUM: Of course they have some pain, but it is not lasting. These children usually had stopped crying before they left the office.

DR. CARROLL S. WRIGHT: Has any one had experience with sodium morrhuate? I have used it extensively and have been told that it does not cause as much pain as quinine hydrochloride and ethyl carbamate and also that there are fewer reactions.

Localized Pemphigus Vulgaris of Eyes, Mouth and Left Breast. Presented by DR. SIGMUND S. GREENBAUM and DR. SIMON KATZ.

E. P., a Negro woman aged 77, presents on the left posterior portion of the hard palate and the right buccal mucosa a nickel-sized area of superficial erosion. There are no blebs in the mouth. In September 1943, such an area developed over the right buccal surface; it was the size of a dime. Recently ten or twelve bullae appeared on the areola of the left nipple, and on Dec. 28, 1943 a soft, granulating, slightly painful, round lesion about the size of a silver dollar appeared, around which several bullae developed. Two years ago the patient noticed a dimness of vision, and three months ago redness, squinting, a moderate degree of lacrimation and burning of the left eye developed. The right eye became involved a month later. Both eyes became progressively worse, with notable narrowing of the palpebral fissures. A vaginal examination on Sept. 17, 1943 revealed no blebs. The blood pressure was 166 systolic and 88 diastolic. Both upper and lower lids increased in thickness, the margins becoming thick, dry and scaly; the conjunctivas on both sides appeared "chewed up" and were replaced by red granulation tissue which extends to the margin of the cornea. The fornices are filled with granulation tissue on a cicatrix with superimposed infection. The pupils are moderately dilated and react poorly to light. The blood sugar level on Jan. 1, 1944 was 175 mg.; a urinalysis on Oct. 15, 1943 showed 2 per cent sugar and on Jan. 14, 1944 0.6 per cent. A blood count on Jan. 6, 1944 revealed a hemoglobin content of 66 per cent and 3,840,000 erythrocytes, but other values were normal. A biopsy specimen from the right eye showed a chronic inflamed nodule with capillaries and variable cellular infiltrate. The patient has been treated with vitamin A, brewers' yeast, riboflavin and penicillin.

DISCUSSION

DR. J. V. KLAUDER: This is a typical case of pemphigus of the eye. I do not appreciate the terminology that Dr. Greenbaum and Dr. Katz have used. I think it should be called pemphigus of the mucous membrane with conjunctival involvement (Klauder, J. V., and Cowan, A.: Ocular Pemphigus and Its Relation to Pemphigus of the Skin and Mucous Membranes, *Am. J. Ophth.* **25**:643, 1942). The onset occurred in the eye; this is rather characteristic of a large percentage of these cases. Subsequently the mucous membranes are affected and then the skin. On the skin it is usually the localized type. At times, however, it is generalized and the patient dies of what appears to be ordinary pemphigus of the skin. The condition of the eye has advanced more in two years than is usual. I think that the woman has had the disease for many years without knowing it, antedating the time her vision was impaired. All mucous surfaces should be examined to see if there is any cicatrization, since the same process that affects the eye also occurs on other mucous membranes. It is a shriveling process, leading to cicatrization and atresia.

DR. CARROLL S. WRIGHT: The history states that the vagina was examined for blebs and none were found.

DR. J. V. KLAUDER: I should feel better satisfied if it were stated that there was no evidence of cicatrization.

DR. SIGMUND S. GREENBAUM: I think Dr. Klauder's criticism regarding the name used here is a good one, but I doubt whether one would find any cicatrices now because these cutaneous and oral lesions developed within the last eight weeks. She has been under observation in the hospital for two months, partly in connection with penicillin therapy. This case would fall in the group of cases of benign forms of pemphigus vulgaris limited to the mucous membranes and in time extending to the skin. In other cases of essential shrinkage it is years before the skin becomes involved. When blebs developed on the left breast, I planted pure cultures of Penicillium notatum over the entire breast, covered them with perforated cardboard for aeration of this saprophyte, and left them on for a week. At the end of the week the cultures of penicillium had completely disappeared and there was an irritating discharge which ran down over the breast and abdomen. Nevertheless, I continued to use them for four weeks, at the end of which time she had an eroded, probably chemical, rather than infectious, dermatitis in addition to the pemphigus vulgaris. The organisms were completely destroyed, presumably by the discharge. Dr. Chester S. Keefer, Chairman of the Committee on Chemotherapeutics, has written me that penicillin, so far as he knows, has not been used for that type of skin disease and that he does not believe it would have any value. However, I have recently seen a patient treated with penicillin by Dr. John Ludy in whom the results were as remarkable as the unique result in a similar case of Schamberg's following colonic irrigation.

Acute Hepatitis with Jaundice Following the Administration of Neoarsphenamine. Presented by DR. SIGMUND S. GREENBAUM and DR. LOUIS GOLDSTEIN.

G. F., a Negro man aged 55, presents skin of a distinct yellowish tint with a generalized papulosquamous eruption and excoriations. On the lower extremities there are many superficial scars of long duration. The pupils react to light and in accommodation; the sclerae are icteric. The patient has been addicted to alcohol for many years. In 1925 the serologic tests on his blood for syphilis were positive and he then received three injections into an arm with no ill effects. Until recently his general health was good. During a routine examination his blood was found to have a positive reaction for syphilis. He was referred to his family physician for antisyphilitic therapy. In all, he received three weekly injections of neoarsphenamine of 0.45 Gm. each. A few hours after the last injection he began to have chills, followed by fever and pain in his epigastric region, and within a week a generalized jaundice and pruritus appeared, followed by a papular dermatitis. The abdomen is distended and the spleen moderately enlarged. The upper border of the liver is palpable in the seventh interspace in the midclavicular line. The

lower edge cannot be definitely felt, but it is presumed to be about 1 inch (2 cm.) below the costal margin in the midclavicular line.

A urinalysis showed a faint trace of albumin and dextrose and a positive reaction for urobilin in a 1:20 dilution. The feces showed no abnormalities. A gastric analysis revealed hyperacidity. A complete blood count disclosed 63 per cent hemoglobin, 3,850,000 erythrocytes and 7,000 leukocytes, of which 62 per cent were neutrophils, 2 per cent eosinophils, 1 per cent monocytes and 35 per cent lymphocytes. The coagulation time was five seconds; platelets numbered 173,250. As to fragility, hemolysis began at 0.46 per cent and was complete at 0.30 per cent.

A chemical examination of the blood showed the following values: dextrose, 113 mg. per hundred cubic centimeters of blood; urea nitrogen, 17 mg.; uric acid, 6.5 mg., and chlorides, 580 mg. The carbon dioxide capacity of the plasma was 51 volumes per cent. The cholesterol content of the blood serum was 390 mg.; the total protein content, 7.36 mg.; the albumin content, 3.98 mg. and the globulin content 3.38 mg. per hundred cubic centimeters. The phosphatase activity was 1.6 units; the van den Bergh test (indirect) showed a bilirubin content of 1.6 mg. per hundred cubic centimeters.

The Wassermann reaction of the blood was negative.

DISCUSSION

DR. SIGMUND S. GREENBAUM: The gastroenterologists admitted this patient to their service as having arsenical hepatitis. I think that he has a hepatic Herxheimer reaction and presented him for discussion on that basis.

DR. LOUIS GOLDSTEIN: I do not believe that this is a Herxheimer reaction, because a syphilitic lesion is prerequisite to such a reaction. In this patient the evidence of syphilis is based on a positive Wassermann reaction of the blood discovered accidentally eighteen years ago. His hepatosplenomegaly of unknown duration is not likely to be syphilitic in origin, for it could have been caused by either alcoholism or his present reaction. Hanger and Gutman (*J. A. M. A.* **115**:263 [July 27] 1940) described a series of cases of postarsphenamine jaundice which they classified into two groups, the obstructive and the hepatitic. This particular case fits into the group of cases of the obstructive type. In the latter, the reaction occurs after the second or third injection, with an interval of one to two weeks between the first injection and the reaction. Thus, the reaction phenomenon is not that of a Herxheimer effect but of drug sensitization. In these cases there are jaundice and intense pruritus at the onset. There also appear a moderate anemia and an enlargement of the spleen and liver, and while the gastrointestinal symptoms subside the anorexia and moderately elevated temperature continue for some time. All these criteria are present in this case. Finally, the obstructive type is differentiated from the nonobstructive variety by the elevation of the blood cholesterol level. I believe, therefore, that this is a case of obstructive jaundice due to sensitization.

DR. VAUGHN C. GARNER: To a dermatologic group it is hardly necessary to point out the moral to be drawn from this case, but it is regrettable that the general profession is not familiar with the fact that for latent syphilis all treatment should be started with heavy metal rather than with arsphenamine. I have seen a comparable case, that of a young man whose Wassermann reaction was discovered to be positive by his draft board and who was given neoarsphenamine without any preparation by his physician. Subsequent to the third injection, a profound jaundice developed with an extreme degree of fever and illness and a generalized toxic erythema. The patient was extremely ill for a number of weeks, and the physician, frightened by this reaction, referred him to me for continuation of treatment. He has done extremely well with bismuth therapy. It is regrettable that the profession in general regards the discovery of a positive Wassermann reaction as synonymous with the need to administer arsphenamine.

DR. SIGMUND S. GREENBAUM: I am interested in Dr. Garner's starting his patient with a heavy metal while he still had the jaundice.

DR. VAUGHN C. GARNER: I waited until he recovered. But he has since had forty injections of the bismuth preparation, which he has tolerated perfectly well.

DR. SIGMUND S. GREENBAUM: If, as I think, this patient has a Herxheimer reaction, there is undoubtedly severe swelling of the hepatic cells at the site of the syphilitic infiltrates, thus causing an obstruction of the ducts. Of the hundreds of cases of acute syphilis treated with tremendous doses or massive arsenical therapy in recent years, the reports on the complications of this type of treatment indicate that hepatic intoxication is the rarest of all complications. In 1919 I saw at least a dozen such patients in the Hospital of St. Louis in Paris in the outpatient service of Dr. Milian. As is well known, he made a distinction between the Herxheimer reaction and the type which he thought might be arsenical. It is hard to conceive of three doses of 0.45 Gm. a week apart reaching the liver in so heavy a dose as to produce an arsenical hepatitis of this sort, because it is known that arsenic is eliminated rapidly and largely through the skin and other organs rather than through the liver. However, I have seen 2 cases of arsenical hepatitis with acute yellow atrophy and death. Although Milian generally continued arsenical therapy in cases such as I have just presented, I think it the better part of valor to stick to iodides and bismuth injections.

DR. EDWARD F. CORSON: Would Dr. Garner dare give arsenic again to his patient?

DR. VAUGHN C. GARNER: I have hesitated to do so. The serologic reactions of my patient's blood are now negative and the reactions of the spinal fluid are negative; hence I feel that a reasonable amount of heavy metal therapy should suffice, and I would not be justified in taking a chance with arsphenamine.

Tuberculosis Cutis; Lupus Vulgaris. Presented by DR. J. M. SCHILDKRAUT (Trenton, N. J.).

N. S., a white woman aged 28, of good general appearance, presents on the outer side of the left arm a red area about 1.5 cm. in diameter covered with an adherent scale. To the left of this there is a pea-sized, scaling, slightly elevated lesion. On the right breast there is an area about 4.5 by 3 cm., irregular, slightly depressed, with an adherent scale. The borders are moderately inflamed. The right border is made up of small nodules. Similar papular or nodular slightly scaly yellow and brown lesions are found adjacent to this lesion. On diascopic pressure this nodule appears yellowish brown and infiltrated. The patient's father was in a sanatorium for tuberculosis about three years ago. In April 1942, the patient noticed a "pimple" on the left arm, which she picked. It became larger, and she then applied ointments, without effect. The area increased in size, and another smaller nodule appeared

adjacent to the first in January 1943. Another lesion developed on the right breast below the nipple in April 1943.

DISCUSSION

DR. MORRIS MARKOWITZ: There were no nodules present on the breast, and the lesions on the eye would suggest a diagnosis nearer to lupus erythematosus.

DR. J. M. SCHILDKRAUT (Trenton, N. J.): I saw the patient first only a few days ago and thought that I could make out some pinhead-sized nodules on the borders of the breast. I thought that on the left arm there were some small nodules. The lesion on the eye is probably not related to the other eruption. It seems to be a capillary enlargement of the vessels of the conjunctiva of the lower lid which has extended over to the margin of the lid. I do not know whether it is a nevus or what it may be.

COMMANDER H. E. TWINING (MC), U.S.N.R.: I thought that it was lupus vulgaris.

DR. HERBERT J. SMITH: I thought it tuberculosis of some sort.

DR. J. V. KLAUDER: It impressed me more as lupus erythematosus than lupus vulgaris. I think the lesions of the eye are similar to those one occasionally sees in lupus erythematosus affecting the lower lid.

DR. J. M. SCHILDKRAUT (Trenton, N. J.): That is rather an odd distribution for erythematous lupus.

DR. J. V. KLAUDER: I have a patient with lesions on the body and none on the face but, curiously, with some lesions on the palms.

DR. THOMAS BUTTERWORTH, Reading: I subscribe to the diagnosis of lupus erythematosus.

A Case for Diagnosis. Presented by DR. CARROLL S. WRIGHT.

J. R., a white girl aged 8 years, for several months has had a growth on the left side of the nose which has gradually increased in size. Examination revealed a pea-sized indurated elevated nodule. The patient has received one roentgen ray treatment of 140 r through a 0.5 mm. aluminum filter and has been given cottonseed oil locally. The lesion was diagnosed as granuloma annulare, but the case is presented to the society as a case for diagnosis.

DISCUSSION

DR. FRITZ CALLOMON (by invitation): The diagnosis of granuloma annulare appears thoroughly justified. The location is unusual but not exceptional. However, the presence of a central depression makes one think also of the possibility of an epithelioma, even in the case of this strong, healthy-looking child.

The demonstrated case is an instance of a type of lesions which occur in completely healthy persons, without personal or familial evidence of tuberculosis. The much discussed relationship between granuloma annulare and tuberculosis, based on observations of the coincidence of both diseases and the occasional combination of granuloma annulare with papulonecrotic tuberculids, has not yet been completely cleared. Spontaneous disappearance or complete disappearance of an entire eruption following the local treatment of only one or a few lesions (by roentgen ray, radium or solid carbon dioxide) has been observed also in cases of granuloma annulare.

As long as the cause of granuloma annulare is not clear, every observation of etiologic significance becomes important. In this respect may I refer to my own observation of familial occurrence of granuloma annulare simultaneously observed in a mother (60 years of age) and a daughter (27 years of age) without evidence of tuberculosis in either patient or in any other member of the family (*Dermat. Wchnschr.* **82**:317, 1926)? A similar observation was published by Schubert in the same journal (**86**:381, 1928) in a mother 34 years of age and a daughter 8 years of age. It appears worth while to pay special attention to this point when inquiring into the familial status in cases of granuloma annulare.

DR. J. P. GUEQUIERRE: The infiltration is considerable for either diagnosis. Most of the lesions of granuloma annulare that I have seen were segmented. I can recall one that presented a perfect circle. Because the child is 8 years of age, it does not follow that it cannot be a basal cell epithelioma. I have seen 2 epitheliomas, 1 in a child of 4 years and 1 in a child of 6. A biopsy will settle it.

DR. CARROLL S. WRIGHT: I hesitated to perform a biopsy on this child. When I gave the roentgen ray treatment I thought the lesion was a granuloma annulare, and I have seen them vanish easily. I should not have given such a small dose had I thought of epithelioma.

DR. A. STRAUSS: I agree with Dr. Guequierre that it is an epithelioma.

DR. CARROLL S. WRIGHT: I think Dr. Guequierre is right, that the whole question can be settled with a biopsy.

Mycetoma of the Foot. Presented by COMMANDER H. E. TWINING (MC), U.S.N.R.

J. J., a well nourished white man aged 57, gives a history of having had pneumonia and rheumatism and says that early in 1935 he injured his right foot while at work on a WPA project. The foot swelled, and finally fistulas developed which never healed. In March 1940, while he was at work in the Frankford Arsenal, a box fell on his foot, causing seventy days' disability. He returned to work, but owing to pain and swelling he was admitted to the hospital, where an operation was performed, with the diagnosis of osteomyelitis.

The right foot is now considerably swollen and studded with numerous scars which are the end results of previously draining sinuses. Roentgen examination gave normal results, as did the physical examination, with the exception of the right foot.

A blood count was within normal limits. The Kahn reaction of the blood was negative. The tuberculin test elicited a negative reaction. Results of a urinalysis were normal. Monosporium apiospermum was identified by Dr. Weidman. Several biopsy specimens were reported as indicating the existence of osteomyelitis. The patient has had numerous operations and curettage, sulfonamide drugs internally and locally, roentgen ray therapy, thymol iodide and finally penicillin.

This patient was treated for osteomyelitis for almost four years. Repeated roentgen ray examinations revealed a slow, progressive destruction of bones and joints. He complained of intense pain which would be relieved temporarily by operative measures. About three months ago amputation of the foot was decided on but, as a last resort and without much hope of improvement, penicillin was given a trial. On the third day of treatment pain subsided and drainage decreased, and one week ago all drainage had stopped, there remained no evidence of any sinuses and the patient was putting a certain amount of weight on the foot without discomfort. Whether the disease will remain in its present status, only time will tell. However, before

amputation another course of penicillin will certainly be worth trying.

DISCUSSION

DR. J. V. KLAUDER: This is the first case of Madura foot shown before this society; in fact, 1 of the few reported in North America. I think that Lovejoy reported 1 originating in California.

DR. SIGMUND S. GREENBAUM: Were those cultures of any particular color?

COMMANDER H. E. TWINING (MC), U.S.N.R.: They were gray and dirty brown-yellow.

DR. THOMAS BUTTERWORTH, Reading: Where did he contract the disease? He has not been out of Philadelphia since 1910.

COMMANDER H. E. TWINING (MC), U.S.N.R.: This man received an injury to his foot in 1935 while he was working on a WPA project. The trouble began then with swelling and pain in the foot. He was hospitalized for a considerable time. The swelling finally subsided, but he has had remissions and exacerbations ever since.

Recurring Erythematous Eruption of the Palms and Soles Simulating Erysipeloid of Rosenbach. Presented by DR. JOSEPH V. KLAUDER.

M. B., a white man aged 58, born in Italy, when first seen, in June 1943, had had a recurring eruption which first appeared on one palm, later on the other palm and while under observation, affected the soles. The eruption consisted of oval, rounded, circinate and semicircular erythematous lesions. They were located on the palms, the sides and palmar surfaces of the fingers, the soles and the sides of the feet. Their diameter varied from 3 to 4 cm. The color was purplish red; the surfaces, smooth and nonscaly. The periphery of the lesions was always sharply marginated. Pressure would cause partial blanching. The eruption would disappear and reappear. An outbreak consisting of one or several lesions on the palms and at times on the soles would last a few days and would be followed by new lesions appearing elsewhere. The only subjective complaint was itching. The eruption did not interfere with the patient's work as a shoemaker. Examination of the entire cutaneous surface revealed nothing significant except a fungous infection of the toes. The patient was in good general health. The teeth were in poor condition, and the tonsils were enlarged and inflamed. Examination of the urine and the blood and differential counts showed no abnormality.

DISCUSSION

DR. JOSEPH V. KLAUDER: I have never seen anything like this before. A variety of recurring erythematous lesions have been described, but none recurring on the palms and soles. What he has tonight is a poor representation of the eruption as a whole. I saw many lesions that looked like erysipeloid both in color and in location.

DR. MORRIS MARKOWITZ: One can classify this also as an erythema of the palms and soles due to avitaminosis A and B—erythema palmare et plantare.

Generalized Dermatitis Herpetiformis with Mucous Membrane Involvement. Presented by DR. JOSEPH V. KLAUDER.

F. C., a white woman aged 56, born in Greece, was first seen in September 1943, with a generalized vesicular and bullous eruption of two weeks' duration. It started in June 1943, as a localized vesicular eruption around the umbilicus. In September 1943, the eruption comprised many dozens of variably sized vesicles and bullae affecting the entire cutaneous surface, including the scalp, palms and soles. Many vesicles and bullae were discrete and arose from normal skin. Additional lesions appeared in the form of discoid raised erythematous plaques. On the surface of some of the latter there were vesicles and erythematous macules. Some had a central punctum resembling erythema multiforme—erythematous gyrate lesions. On the upper part of the back there was a grouping of vesicular and papulovesicular lesions. On the hard palate and the buccal mucosa there were a small number of erosive areas which the patient said started as blisters. There was no involvement of the conjunctivas, vagina or anal region. There was no Nikolsky's sign. There was severe itching and complaint of burning sensation. The general health was good. The temperature was normal. The differential blood count was as follows: Polymorphonuclear leukocytes, mature, 54 per cent; stab forms, 13 per cent; eosinophils, mature, 8 per cent; stab forms, 5 per cent; plasma cells, 1 per cent; lymphocytes, 19 per cent. There were moderate anisocytosis, slight poikilocytosis and polychromatophilia. Platelets were normal in size and number.

A patch test with 50 per cent potassium iodide in petrolatum elicited a positive reaction. There was progressive improvement and disappearance of all lesions after treatment, which included a salt-free diet, weekly intramuscular injection of whole blood of the patient's sister and sulfapyridine (oral administration of 2 tablets three times a day). This dosage was gradually decreased to 1 tablet three times weekly, which the patient is now taking. She had gained weight and is without symptoms. The skin now shows only congestive and pigmentary remains of many of the former lesions.

DISCUSSION

DR. SIGMUND S. GREENBAUM: One interesting point in this presentation is the statement that there were lesions in the mouth. There are a number of dermatologists who believe that oral lesions do not occur in dermatitis herpetiformis.

DR. MORRIS MARKOWITZ: Chemical studies should show an increase of chlorides and also eosinophilia.

DR. CARROLL S. WRIGHT: Do you attribute the therapeutic response to the sulfapyridine?

DR. JOSEPH V. KLAUDER: Yes, I do.

Book Reviews

Allergy in Practice. By Samuel L. Feinberg, M.D., with the collaboration of Oren C. Durham. Price $8.00. Pp. 798. Chicago: The Year Book Publishers, Inc., 1944.

This volume is a practical exposition and review of the subject of allergy in the various branches of medicine. It is sufficiently detailed to give the practitioner of medicine and the specialist a working knowledge of the allergic conditions which come to his attention. It adequately covers the major aspects of these subjects.

The essential features of a practical and clinical nature are set in normal-sized type. The experimental and theoretic subject matter is set in smaller type. This method of presentation is of value because the book becomes a ready reference for both the beginner and the specialist in the field. A résumé is presented after each chapter, the advantages of which are obvious.

The chapter on "Pollens and Pollen Allergy" (chapter 6), written by Oren C. Durham, chief botanist of the Abbott Laboratories, is a presentation of the many surveys pertaining to pollen and hay fever plants. The common important plants and pollens causing hay fever are described and illustrated with photographs, and their geographic distribution is charted.

There is a long chapter (16) on the "Treatment of Allergic Diseases," which comprises eighty-three pages. The author presents his own experiences and has exercised good judgment in stressing accepted therapy. The so-called recent improved methods of treatment are discussed. Twelve pages of small type are devoted to elimination and other diets of value to the physician.

Sixty-four pages, which include chapters 20, 21 and 22, are devoted to dermatoses of allergic origin, such as urticarian and angioneurotic edema (chapter 20), atopic dermatitis and dermatophytosis (chapter 21) and contact eczema (chapter 22). Tables listing the materials, percentages and vehicles for patch testing are included in this chapter (chapter 22). In this chapter there is also a long table of contact allergens listed alphabetically with the reference to the literature following each.

The author rightly makes few claims for cutaneous tests in the diagnosis of urticaria, angioneurotic edema and atopic dermatitis but emphasizes the importance of patch tests in the diagnosis of contact and industrial dermatoses.

This is an excellent office reference book; the format is good; the bibliography is extensive, and the cross index of twenty pages is a valuable asset.

The Management of Neurosyphilis. By Bernard Dattner, M.D. Price $5.50. Pp. 420, with 40 figures, charts and tables, and comprehensive bibliography, author and subject indexes. New York: Grune & Stratton, 1944.

This monograph on the management of neurosyphilis is an outgrowth of lectures to postgraduate students. It starts, therefore, with basic information and proceeds gradually to cover the entire field of problems which arise in the treatment of the various forms of neurosyphilis. The book is divided into two parts. The first deals with the technics of withdrawal and examination of spinal fluid; the interpretation and evaluation of the different spinal fluid tests and a discussion of the relationship between spinal fluid findings and clinical status of the patient follows, and the section ends with a discussion of the spinal fluid syndromes characteristic for the various clinical types of neurosyphilis and of the atypical humoral syndromes.

The second part deals with methods of treatment, their application and results. The author first describes in detail all the therapeutic procedures at present in use for the treatment of neurosyphilis. He then surveys the results as they are reported by various authors. Having been associated with Wagner-Jauregg, the originator of malaria therapy, it is not surprising to find the author more in favor of the beneficial effects of fever therapy in contrast to other methods. But his experience does not prevent him in giving just account to all other therapeutic endeavors. A vast amount of books and papers from the world literature is digested and utilized to illustrate special points of discussion. General considerations precede every section which deals with the therapeutic results in dementia paralytica, tabes, meningovascular syphilis, etc. All data are critically sifted, and sound advice given according to the author's own experience. The latter is based on twenty-five years' work in the field, first in Wagner-Jauregg's clinic in Vienna and then in the wards of Bellevue Hospital. There can be no better recommendation than Moore's conclusive remark in his foreword to Dattner's book that American medicine is enriched by such monographic studies as this.

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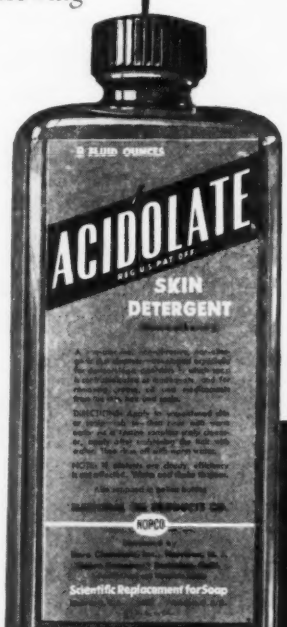

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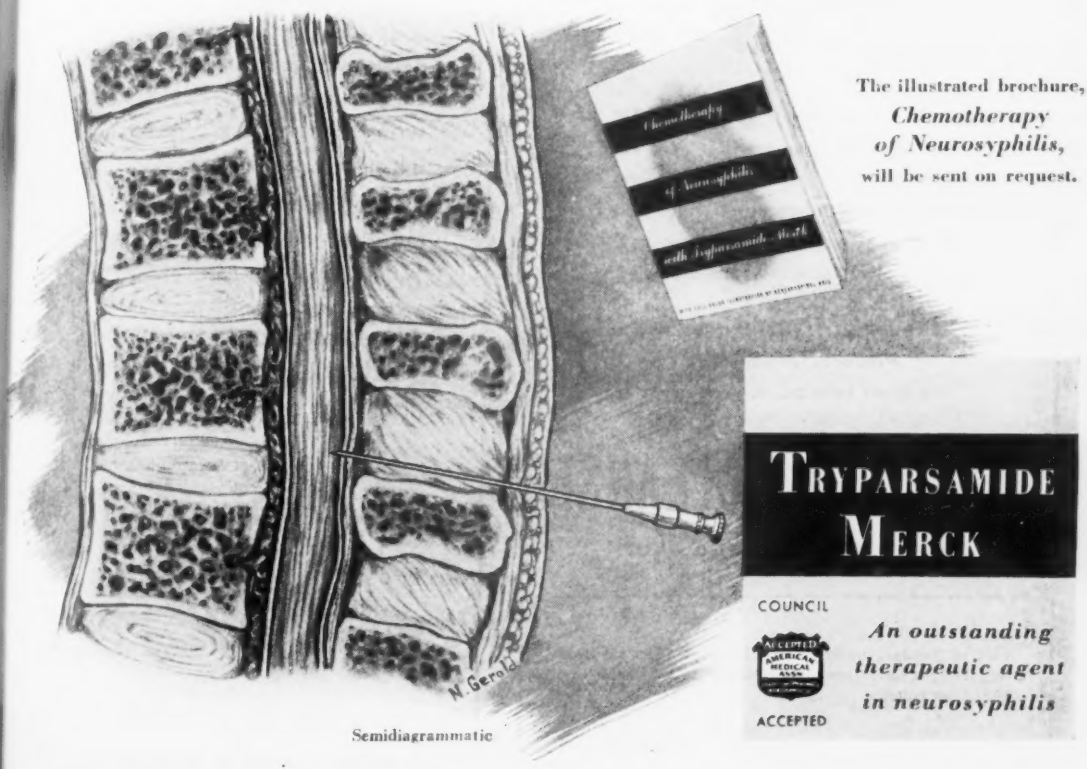

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It doesn't look like much, does it? It could be the torn-off cover of a cardboard box, or a piece of an old magazine, or just some discarded wrapping paper.

But if it is saved and collected, it will become the container for a quart of blood plasma that will save a GI's life. (Every precious bottle of blood plasma is wrapped in corrugated paper to protect it against breakage. Each blood plasma box is made of heavy brown paperboard).

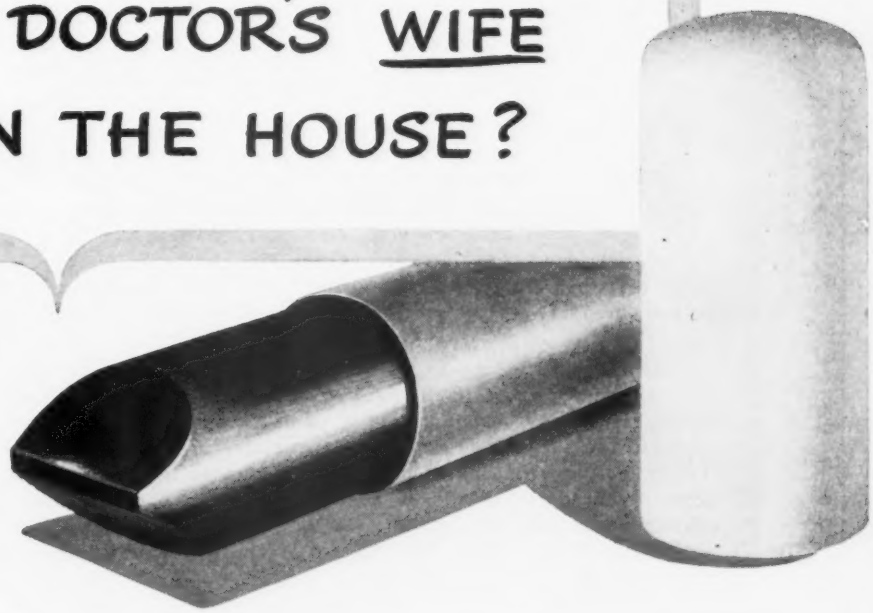
Or it may become part of an airborne container (yes, they're made of paper) *that will drop food or medicine to liberated peoples.*

Or it may show up as the shell case for the shell, or the bomb band for the bomb, that will be the very last explosion to finally shatter the nerve and will-to-fight of the enemy!

Or as the map that points the way for our final breakthrough (our invading forces used more new maps of France, for instance, than the total number made from the beginning of history to 1940!)

So you see, that piece of paper can be pretty exciting. *But only if it is saved.* Our armed forces need every scrap of every kind of waste paper. That goes for paperboard, newspapers, magazines, *every* kind of waste paper. Throw them away and you're throwing away helmet linings, gun covers, ration containers — countless war materials too numerous to mention here. Save every scrap and you'll help end the scrap!

IS THERE A DOCTOR'S WIFE IN THE HOUSE?



We've a message — and a gift — for your wife. We want her to try our preparations. It will take about an hour of her time, and in return for that courtesy we will present her with a Beauty Counselor $1.00 lipstick in any shade she selects.

We believe she will enjoy the hour. But, most important, we hope she will tell *you* about our *try-before-you-buy* method of selection—how each customer has a chance to use these hypo-allergenic preparations, without charge, to see that those recommended really suit her skin.

Please use the coupon below. If, in addition, you would be interested to see formulas, check where indicated.

beauty counselors

beauty counselors, inc., 17108 Mack Avenue, Grosse Pointe 24, Michigan

☐ Send me formulas.

☐ Arrange to give my wife a presentation and a $1.00 lipstick. You will find her at home at

Street_____ City_____ Phone_____

Doctor_____ Address_____

A.D.S.

Luzier Cosmetics and Allergy

Women use cosmetics because they have developed a need for them: they are essential to modern standards of good-grooming and therefore contribute to a sense of well-being. Your patient's appearance, viewed cosmetically, is a factor that deserves your consideration both during hospitalization and convalescence. Cosmetics cannot lift faces, but they certainly perform wonders when it comes to lifting a woman's spirits. Women have an instinctive desire to look pretty and to smell sweet.

Since cosmetics are so universally used it is not to be wondered that they sometimes figure in the field of allergy. That is why when there is a history of allergy we suggest that patch tests be made with those of our products the subject is using or contemplates using. If they test positive, further testing with their constituents is indicated to determine the offending agents. These found, we frequently can modify our formulas to suit the subject's requirements. The patch test is generally considered best for testing cosmetics because it most closely approximates the conditions under which they are normally used.

While our products are free from so-called common cosmetic allergens, such as orris root and rice starch, we feel it should be made clear that any of their normally innocuous ingredients might be allergenic to the allergic individual. It is our practice to write our patrons a letter to this effect when a history of allergy is involved.

It is our experience that many persons with allergic constitutions cannot tolerate scented cosmetics; therefore we routinely recommend and select unscented products when there is a history or suspicion of allergy. This practice is not to imply or suggest that the subject is sensitized to perfume; it is solely to safeguard against the possibility.

In specific cases of allergy or suspected allergy, when the subject is using or contemplates using our products, we are pleased on his request to send her doctor the involved raw materials for patch testing, also such information concerning our products as may have a bearing on the case.

Since in the light of present knowledge it is not possible, save in specific cases, to make non-allergenic cosmetics, we believe the cosmetic requirements of the allergic individual should be considered by her doctor in the light of the formulas and general characteristics of the products she is using or contemplates using.

Luzier's, Inc., Makers of Fine Cosmetics & Perfumes

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LOWILA CAKE contains lauryl sulfoacetate diluted in bentonite. The pH approximates that of normal skin. It is free of all perfume.

LOWILA CAKE is non-irritating, only mildly defatting and of low sensitizing index; cleanses the skin as satisfactorily as soap — at a cost comparable to that of soap.

LOWILA CAKE is an excellent cleanser for general toilet use — including the bath and shaving.

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